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Application of economic evidence in health technology assessment and decision-making for the allocation of health resources in Latin America: Seven key topics and a preliminary proposal for implementation

A report for the Inter-American Development Bank

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Abstract:

This technical note¹ discusses the application of economic evidence in health technology assessments for decision-making on the allocation of health resources. There is already recognition in Latin America that the economic dimensions of health interventions, such as cost-effectiveness and budgetary impact, are critical dimensions that should always be considered when making decisions about the coverage or inclusion of technologies in benefits packages. However, there are still barriers and constraints that prevent the evaluation of economic evidence in the region from being an integral part of all decision-making processes, with serious implications for the equity and efficiency with which health resources are allocated. The purpose of this technical note is to provide elements and tools that contribute, in a practical way, to overcoming these barriers, answering the questions asked by health systems that are beginning to apply economic evidence in their evaluation and decision-making processes. How do we know if a technology or intervention is cost-effective in our context? What cost-effectiveness threshold should be applied? How might non-economic criteria and dimensions influence our cost-effectiveness threshold? What limit should be considered when a technology implies a high budgetary impact in a particular health system? Given the existing difficulties in generating local economic evidence, what can the economic evidence generated in other jurisdictions tell us? How can economic evidence be taken into account in a fragmented health system? Consideration of these aspects is key to ensuring fairer, more transparent allocation of health resources and thus achieving more efficient and equitable health systems in Latin America.

JEL CODES: I10, I11, I13, D61, H51

Key Words: fprioritization, explicit priority setting, economic evidence, cost-effectiveness, budgetary impact, cost-effectiveness threshold, health expenditure, financing with public resources, financing in health, public expenditure in health, public health.

¹ This technical note is based on a report prepared by the authors within the framework of the Inter-American Development Bank's (IDB) technical cooperation with Argentina in 2019. This cooperation involved the active participation of the Criteria Network team of the IDB Social Protection and Health Division (<https://criteria.iadb.org>), under its knowledge generation strategy on explicit priority setting in health.

TABLE OF CONTENTS

ABSTRACT.....2

List of tables6

List of figures.....7

Introduction.....8

References10

HOW TO PRIORITIZE INTERVENTIONS AND TECHNOLOGIES FOR EVALUATION PURPOSES.....12

1.1. Definition of HTA agencies’ mandate and responsibilities as a first priority-setting decision.....12

1.2. Criteria and processes for priority setting13

1.3. Linking priority setting to decision-making processes.....13

1.4. Discussion points for Latin American countries and preliminary proposal of prioritization mechanisms to be taken into account by the agencies14

1.5. Final remarks18

References19

VALUE FRAMEWORKS: DIMENSIONS TO BE CONSIDERED WHEN ASSESSING THE VALUE OF HEALTH TECHNOLOGIES.....20

2.1. Approaches used to assess the value of health technologies.....20

Benefits in clinical outcomes.....20

Cost savings.....21

Public health benefits.....21

2.2. Discussion points for Latin American countries and preliminary proposal of general guidelines for the definition of a value framework.....23

References26

DETERMINING THE OPPORTUNITY COST IN HEALTH.....28

3.1. Estimating the threshold.....28

Threshold estimation based on opportunity cost.....29

Threshold estimation based on current practices of decision-makers29

Threshold estimation based on health spending aspirations29

Threshold estimation based on social preferences30

3.2. Estimating the opportunity cost.....30

3.3. Discussion points for Latin American countries and preliminary proposal of opportunity cost values for countries without their own estimates.....31

What is the best estimate of the opportunity cost in health that can be made in the absence of specific data for a particular health system and country?32

References34

DECISION-MAKING THRESHOLDS AND MODIFIERS37

4.1. Modifiers to the decision in the deliberative process.....37

4.2. Modifiers reflected in the use of “differential” thresholds.....38

4.3. Discussion points for Latin American countries wishing to establish a decision-making rule for the inclusion of technologies39

 Potential implications of the use of modifiers in decision-making 39

4.4. Example of a decision rule and modifiers 40

 A - Health technologies or interventions that are cost-saving or are clearly cost-effective according to the local opportunity cost threshold.....42

 B - Health technologies or interventions that perform well in dimensions considered relevant according to the local value framework and that could be covered despite lack of an optimal cost-effectiveness profile43

 C - Special cases of effective health technologies or interventions for severe life-threatening diseases that may not be cost-effective according to the local opportunity cost threshold43

 D - Special cases of effective health technologies or interventions for severe ultra-rare, serious life-threatening diseases that may not be cost-effective according to the local opportunity cost threshold.....44

4.5. Application in Latin American countries..... 44

4.6. Final remarks.....46

References46

BUDGETARY IMPACT AND AFFORDABILITY THRESHOLD48

5.1. Addressing aspects of affordability.....48

5.2. Discussion points for Latin American countries.....49

5.3. When can we say that a technology has a high budgetary impact? Preliminary proposal for a baseline budgetary impact threshold for countries and health systems that have not made their own estimates50

 International estimates of what is considered high budgetary impact 50

 Preliminary estimate of a budgetary impact threshold for jurisdictions without their own estimates..... 51

5.4. Final remarks.....54

References54

USING ECONOMIC EVIDENCE FROM OTHER JURISDICTIONS57

6.1. Key elements of the data to be used57

6.2. Interpretation and use of HTAs conducted in other jurisdictions.....58

6.3. Abbreviated “rapid screening” process for low- and middle-income countries....58

6.4. Discussion points for Latin American countries.....59

6.5. Preliminary proposal for a provisional or temporary approach to estimate the likelihood that a technology will be cost-effective in the absence of local economic assessments.60

 Analysis of coverage or inclusion of technology in the benefits packages of other countries.....61

 Crude extrapolation of the cost-effectiveness of economic evaluations (EE) conducted in other jurisdictions63

 Estimation of a “cost-effect ratio” based on the results of clinical studies.64

How to consolidate the information surveyed?65

Economic evidence could be considered favorable to the inclusion of technology under the following conditions:65

Economic evidence could be considered unfavorable to the inclusion of technology under the following conditions:66

6.6. Final remarks.....66

References67

IMPLEMENTATION OF HTAs IN FRAGMENTED HEALTH SYSTEMS.....69

7.1. Challenges in fragmented health systems.....69

7.2. Discussion points for Latin American countries and preliminary proposal of a methodology for estimating the opportunity cost in different health subsectors70

 Tailoring thresholds to different subsectors within the same country71

7.3. Final remarks.....72

References73

APPENDIX I - Preparation of the preliminary report for Argentina74

LIST OF TABLES

Table 3-1 Estimates of opportunity cost in different countries: sources, ranges, and estimates in units of GDP and health expenditure per capita.....32

Table 3-2 Estimates of the opportunity cost in different Latin American countries, extrapolated from the results obtained in international studies (US\$ 2016 and, in parentheses, fraction of GDP 2016).....33

Table 4-1 Ranges in which the cost-effectiveness of a healthcare technology in each category (expressed as multiples of opportunity cost - OppC) could be considered acceptable41

Table 4-2 Threshold or upper limit for considering the cost-effectiveness of a health technology acceptable in each category (in US\$ 2016 and as a fraction of GDP)45

Table 4-3 Benefits obtained, benefits lost, and net benefits from covering technologies at the upper limit of each category46

Table 5-1 High budgetary impact threshold in selected countries52

Table 5-2 Estimates of the high budgetary impact threshold for different Latin American countries (in constant 2016 US dollars), expressed as total net value at the country level, per million inhabitants and as equivalent in number of additional inhabitants who could receive coverage.53

Table 6-1 Probability that the technology is cost-effective in the local context (for this particular indication in this group of patients). Example of a hypothetical case.....61

Table 7-1 Estimate of opportunity cost threshold and budgetary impact by subsector in Argentina (US\$ 2016).....72

Table 7-2 Threshold or upper limit to consider the cost-effectiveness of a health technology acceptable in each category in the different health subsectors in Argentina: central estimate and lower and upper limit (US\$ 2016 and as a fraction of GDP).....72

LIST OF FIGURES

Figure 2-1 Potential elements of value that could be considered in economic assessments 22

Figure 4-1 Different cost-effectiveness thresholds of decision making and their relationship with the opportunity cost threshold, by health technology category..... 41

Introduction

Health systems around the world must now operate under increasingly complex political, economic, and technical conditions: rapid technological change, pressure to introduce new preventive, diagnostic, therapeutic, or rehabilitation interventions, an aging population, and health budgets that account for larger proportions of countries' gross domestic product each year.

The countries of Latin America have achieved significant health gains in recent decades, with steady progress toward universal health coverage (UHC) throughout the region. Nonetheless, health systems in Latin America face the same complexities today as those in the rest of the world, compounded by the persistence of significant inequities, inefficiencies, and suboptimal health outcomes (Dmytraczenko, 2015; Cotlear et al., 2015; Atun et al., 2015).

Among the action that the governments of most Latin American countries have taken to tackle these challenges is the creation of health technology assessment (HTA) programs, units, or agencies that participate, with a greater or lesser degree of institutionality, in decision-making on health resource allocation. This process involves deciding which technologies and interventions will be covered with their health system's limited resources or included in benefits packages.

How to make these difficult decisions as fairly as possible is, or should be, a major concern of health decision-makers. Selection of the criteria and dimensions to be considered when assessing the value of health technologies and decisions on their coverage or inclusion in benefits packages should reflect the overall objectives of the health system (e.g., the maximization of population health and financial protection), as well as other values relevant to society (i.e., equity, solidarity, access to quality health care) (Oortwijn 2019). Virtually without exception, in all explicit decision-making processes in the region, the effectiveness and safety of technologies and interventions are key dimensions that must be rigorously assessed before making a coverage decision. However, there is also agreement in Latin America and the world over that if the goal is to maximize health, or more broadly, maximize population well-being, evaluating effectiveness and safety is not enough to achieve fairer, more efficient health systems.

There is general recognition in Latin America that the economic dimensions of technologies, such as their cost-effectiveness and budgetary impact, are critical dimensions that should always be evaluated and considered before making a coverage decision (Pichon-Riviere et al., 2019). However, there are still barriers and constraints that prevent the evaluation of economic evidence from being an integral part of all decision-making on the allocation of health resources in the countries of the region. This has serious implications for both equity and the efficiency with which health resources are allocated in Latin America.

Because resources are limited, the decision to cover or include a particular technology in the benefits package implies that those resources will not be available for other technologies or interventions, or that resources will have to be shifted from interventions currently covered, making them no longer available or less accessible. Thus, an evaluation and decision-making process that does not consider both the costs and benefits of interventions and does

not permit comparison of the relationship between the cost and benefits of the different alternatives will not be able to account for these aspects. This is true for low- and high-income countries alike, as all without exception face budgetary constraints. Paradoxically, it is often high-income countries that have stricter structures, mechanisms, and processes for prioritizing the services to be financed with public resources.

While several Latin American countries have for years made the assessment of economic evidence (mainly cost-effectiveness and budgetary impact) a requirement in their decision-making processes (Augustovski et al., 2015), there are still barriers that limit the scope of these assessments. This implies suboptimal decision-making processes that in many cases end up with unfair and inefficient implicit rationing, resulting in low coverage of priority cost-effective services in several countries of the region, with some of the resources allocated to expensive and inefficient non-priority services.

This technical note discusses the application of economic evidence to health technology assessment and decision-making on health resource allocation. The objective is to provide a series of key elements and tools that help pave the way for countries or health systems in Latin America that are making progress in strengthening their decision-making processes.

Specifically, it seeks to provide practical answers for some of the questions that health systems ask when beginning to apply economic evidence in their decision-making on the coverage of technologies and their inclusion in benefits packages: How can we know whether a certain technology or intervention is cost-effective in a particular context? What cost-effectiveness threshold must be applied? What other criteria and dimensions, beyond the economic, could influence the cost-effectiveness threshold? When does a technology to imply a high budgetary impact in a particular health system? How can the economic dimension be taken into account when no studies have been conducted in the jurisdiction in question? How can economic evidence be taken into account if the country has a fragmented health system?

With these elements, we hope to contribute to overcoming some of the barriers that limit the effective use of economic evidence in decision-making on the allocation of health resources in the region. This technical note discusses seven key issues. The first two chapters, deal with more general topics. Chapter 1 discusses how to prioritize the technologies to be assessed, since any assessment requires time and effort, and it is essential that health technology assessment (HTA) agencies make efficient use of their own resources. For this, the chapter proposes elements and tools to consider when prioritizing. Chapter 2 discusses value frameworks, seeking to define the dimensions that should be considered when assessing the value of health technologies. For transparent and legitimate evaluation and decision-making, it is essential to explicitly define the criteria and dimensions to consider, including the importance of economic dimensions such as cost-effectiveness and budgetary impact. This chapter presents international and regional experiences and elements that can guide this process.

The five remaining chapters are related to specific aspects of the evaluation of the economic dimension. Chapter 3 analyzes how to determine the opportunity cost in health, the most important reference to consider when determining whether a technology or intervention is cost-effective in a particular health system, and proposes a methodology for estimating the opportunity cost in health for each of the countries of the region. Chapter 4 analyzes thresholds and modifiers of decision-making, discusses how different countries and health

systems take dimensions other than the economic into account when assessing the value of technologies, and proposes a frame of reference for countries that are developing their decision-making processes. Chapter 5 discusses the dimension of budgetary impact and affordability. Based on international experiences, it proposes methodologies and reference values to enable Latin American countries to set the values that should determine whether a certain technology or intervention could represent a high budgetary impact. Since many countries may struggle to obtain local economic evidence, Chapter 6 presents mechanisms for taking advantage of economic information and evidence from other jurisdictions. Finally, Chapter 7 analyzes how to evaluate and apply economic evidence in fragmented systems (with public subsystems for provinces, states, or regions or subsystems for social security or private systems, etc.); it also proposes tools for tailoring the available information to existing decision-making processes.

This technical note is based on a report produced by the authors in 2019 at the request of the Inter-American Development Bank (IDB) on the use of economic evidence for making coverage decisions for Argentina. It discussed some key technical issues at the time that a health technology assessment agency could face in its initial years, especially the use of economic evidence for decision-making on the allocation of health resources. This report benefitted from the active technical support of the IDB team and its Criteria Network.

The authors wish to thank the institutions and experts who participated in the working meetings for the preparation of that first report, whose ideas and contributions enriched the discussions and gave rise to much of the material presented in this technical note. See the Annex for further information.

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1. HOW TO PRIORITIZE INTERVENTIONS AND TECHNOLOGIES FOR EVALUATION PURPOSES

Even the richest, most developed countries do not have the resources and technical capacity necessary to assess all health technologies. Priorities must therefore be set – ideally, through an explicit process – to determine what will be assessed with the available technical and financial resources. This is particularly important in low- and middle-income countries that have fewer resources to conduct health technology assessments.

In addition to the need to make efficient use of the resources of HTA agencies, since all technologies will not be evaluated, there is a risk of producing serious distortions in decision-making on the use of health resources unless there are clear and explicit mechanisms to guide the prioritization process (Drummond et al., 2008). Determining which technologies will be evaluated can influence the final coverage decision as much as the evaluation process itself.

The first part of this chapter discusses some of the most important aspects of the prioritization process. It then presents a series of key elements to be considered when establishing and implementing prioritization processes for the technologies to be evaluated by HTA agencies, with a particular focus on low- and middle-income countries.

1.1 Definition of HTA agencies' mandate and responsibilities as a first priority-setting decision

Health technologies include the medicines, devices, procedures, and organizational systems that are used in the health system. One of the first decisions to be made when establishing an HTA agency, therefore, is whether it will have responsibilities for a wide range of technologies.

Some of the HTA agencies around the world that conduct assessments to inform pricing and reimbursement decisions, such as Australia's PBAC (Pharmaceutical Benefits Advisory Committee) and Scotland's SMC (Scottish Medicines Consortium), focus solely on medicines. The responsibilities of other agencies focus on the needs of a particular organization – for example, Germany's IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in the Health System]) which responds to the needs of national health insurance (the Krankenkassen). Other agencies have broader responsibilities. For example, NICE (National Institute for Health and Care Excellence) in the United Kingdom has programs to evaluate medicines, devices, public health interventions, and social assistance programs. Ideally, the HTA agency in a particular jurisdiction should evaluate a wide range of technologies, as there is no reason to believe that inefficiency in resource use is differentially associated with some types of technology rather than others (Drummond et al., 2008).

Other aspects of an HTA agency's responsibilities that will need to be defined from the outset include determining whether it will be responsible only for making recommendations on the inclusion or reimbursement of technologies, or also for regulating or negotiating prices or whether its recommendations will be mandatory or merely "advisory."

Each country's decisions on how the HTA agency will be structured, what its mandate and responsibilities will be, and, above all, how HTA will be linked to the decision-making process are the basic elements that will determine the characteristics of the HTA agency in each jurisdiction.

1.2. Criteria and processes for priority setting

Once the HTA agency is up and running, it is to be expected that, sooner or later, evaluation needs will exceed the available resources and capacities. Thus, the need to prioritize which evaluations will be carried out first is inevitable. In many low- and middle-income countries that begin their HTA process late, this situation is often present from the moment the HTA agency is established, as it must deal with a pent up unmet demand for evaluations.

Prioritization of the technologies and interventions to be evaluated involves different elements: identification of the important problems for decision makers, identification of technologies that could respond to priority health needs or problems, identification of possible evaluations that could help decision makers, and rendering a judgement about the potential benefits and costs of possible evaluations and determining their priority (Henshall et al., 1997).

While no two countries, agencies, or health systems in the world prioritize interventions the same way, and no criteria can be considered universal or standard procedures, most HTA agencies appear to take certain common elements into account.

Noorani et al. studied the procedures followed by 11 HTA agencies from 10 countries when prioritizing the technologies to evaluate. Their goal was to identify the criteria on which these decisions were based. They found that the most common criteria were related to both clinical and economic impact (cost-effectiveness and budgetary impact). Other frequently mentioned criteria were the burden of disease that the technology aims to address, the expected level of interest in the evaluation, the availability of scientific evidence, the timeliness of the evaluation (its appropriateness, based on decision-making times), and the degree of controversy surrounding the technology and the variability of its use (Noorani et al., 2007).

A systematic review of the literature and websites of all European HTA INAHTA (International Network of Agencies for Health Technology Assessment) member agencies found that criteria most often used to prioritize the technologies to evaluate were their potential benefits, costs, and cost-effectiveness and the burden of disease (Specchia et al., 2015).

A 2017 review by Varela-Lema et al. found that most HTA agencies seemed to consider eight critical domains when prioritizing the technologies to evaluate: 1) need for intervention; 2) health outcomes; (3) the type of benefit from the intervention; (4) economic implications; 5) existing knowledge about the intervention/quality and uncertainty of the evidence; 6) implementation and complexity of the intervention/feasibility; (7) priority, justice, and ethics; and 8) global context (Varela-Lema et al., 2017).

1.3. Linking priority setting to decision-making processes

In some jurisdictions, there is a link between the selection of technologies to be evaluated

and the decision-making process. For example, in the Netherlands, new drugs that are similar to existing drugs on the market are not prioritized for a full formal evaluation. Once a rapid evaluation of their effectiveness determines that they are clinically equivalent to other options available in the country, they are assigned a reference price based on existing drugs without being subject to a more thorough evaluation (for example, cost-effectiveness studies are unnecessary). Conversely, if the manufacturer or sponsor of the technology claims that the product has advantages that would justify a higher price, a more detailed evaluation of the drugs is conducted.

Similarly, in England, new technologies that are clearly more cost-effective than NICE's threshold of £20,000 per QALY are not subject to a detailed HTA and are usually included. Something similar happens with medical devices that save costs to the National Health Service.

In more general terms, prioritization of the technologies to be evaluated should consider the type of hearing to be held for the HTA documents and the decision-making responsibilities of that hearing. The clearest situation is when there is a committee that determines what treatments will be included in the benefits or coverage form or package. Since in these cases, the committee has a clear need for information and the ability to act on the results and recommendations of the HTA, the prioritization process for the initial evaluation of technologies should take these needs into account.

1.4. Discussion points for Latin American countries and preliminary proposal of prioritization mechanisms to be taken into account by the agencies

The following are some of the questions that may arise when defining the mechanisms for prioritizing the technologies to evaluate.

- (a) What will the HTA agency's mandate and responsibilities be? This involves clearly indicating which technologies are within its scope and which are not, bearing in mind that they should ideally cover a wide range of technologies (e.g., medicines, devices, procedures, public health and social assistance programs). At the same time, it also involves specifying the type of decisions that will be informed by the HTA, its audience, and its decision-making responsibilities.
- (b) Should the possibility of establishing a procedure for active identification of the technologies to be evaluated be considered? These procedures, sometimes known as horizon scanning, can be performed for different purposes – for example, the early identification of technologies that could have an impact on the health system, or ensuring that the list of candidate technologies to evaluate is aligned with national health priorities or includes technologies and interventions with high potential social value (Oortwijn W, Jansen M, 2019). Particularly in low- and middle-income countries, the most valuable technologies to include in benefits packages are not necessarily the newest. Potentially effective and cost-effective technologies, such as some preventive programs, will not necessarily have a sponsor to request and promote their evaluation and may not be considered for evaluation by agencies in the absence of active mechanisms to detect and include them in the lists of technologies to be evaluated.

(c) Finally, is there a desire to establish an explicit procedure for prioritizing evaluation issues? While this is internationally recognized as a fundamental principle of good practice in HTA and is necessary to strengthen the legitimacy of decisions that will be informed by it, it has organizational and political implications. For example: resources are required to take it forward, and some decision-makers may view it negatively, as it could reduce their discretionary framework for decision-making.

Once it has been determined that a mechanism should be established for prioritizing the issues to evaluate, it should be noted that there are different levels in the decision-making process where this prioritization can be applied. As already mentioned, HTA agencies and health systems almost never have the capacity, or the mandate, to immediately evaluate all health technologies that receive regulatory approval. This implies that many technologies are often available in the country that have not yet been evaluated and whose coverage and/or inclusion in the benefits package has not yet been decided.

For example, the Constitution of the National Health Service of England (NHS) states that patients are entitled to receive drugs or treatments approved by assessments conducted by the HTA agency (NICE) if recommended by their doctor. For drugs or treatments that have not yet been evaluated, it states that coverage decisions should be “rational and evidence-based.” This generates few conflicts in countries such as England, in which the indication and request for coverage of technologies not approved by the HTA agency is rare, and where the HTA agency also has the capacity to evaluate and decide on all potentially conflicting technologies.

In low- and middle-income countries, such as those of Latin America, the gap between available technologies and those explicitly evaluated and covered or defined in the benefits package is usually greater, and this can undermine the legitimacy of coverage decisions or the benefits package. It is also often one of the roots of the judicialization of the right to health confronting several countries in the region. For example, the PMO (Compulsory Medical Plan) in Argentina clearly indicates the medicines, devices, and procedures whose accessibility must be guaranteed to beneficiaries of the national social security and private systems (which provide coverage for approximately 20 million people, about half the population). However, the lack of clear mechanisms for updating the explicit package of coverage has made it simply the definition of the minimum coverage floor, leaving all the new technologies that have not yet been evaluated in limbo. Given this situation, while it is clear that there is mandatory coverage of all the technologies included in the benefits package (PMO), it is not clear that those that have not been evaluated and are not explicitly included in the package should not be covered. Denying coverage of a technology simply because it has not been evaluated and is not included in the PMO ends up being an argument that is not considered legitimate, either by society or the justice system, given the lack of explicit mechanisms for updating the PMO. Health funders are in the worst possible situation: required to provide everything included in the PMO but at the same time exposed to the demand for coverage of all technologies that have not yet been evaluated, which usually are precisely the newest, most controversial, and expensive technologies.

As mentioned at the outset, prioritizing the technologies and interventions to evaluate implies that there will be technologies that will not be evaluated, at least for a certain period. This is correct and is precisely what gives meaning to the notion of prioritizing. However, especially in countries in the early stages of implementing health technology assessment processes, prioritizing assessments can be perceived as one more strategy for limiting

coverage: the technology is not evaluated and therefore not covered.

To lend more legitimacy to the process, it is valid to consider mechanisms that assure the population that things that are “really important” will be identified. In this context, it may be useful to establish active prioritization procedures that guarantee the various social actors (i.e., users, the judicial system, industry, patients) that all technologies and interventions that represent a potentially high value for society will be evaluated as a priority, and that a decision on their coverage will be made within certain reasonable deadlines (for example, less than 6-12 months from their regulatory approval or the request for their inclusion in coverage). The definition of “really important” or “of high value to society” will vary from jurisdiction to jurisdiction and is discussed in the next chapter on value frameworks.

Having such a mechanism cannot only enable the benefits package to serve as a list of everything that must be covered, but would give it the legitimacy to determine the non-compulsory coverage of technologies not on the list.

With all this in mind, the following could be some of the criteria to consider in identifying technologies that should be given high priority for evaluation:

- There is reasonable certainty (lower threshold of 95% confidence interval [95% CI] in clinical trials) that the technology can offer patients with serious life-threatening diseases additional survival of at least 3 months, or its equivalent in quality-of-life improvement (at least 0.2 QALYs). This category could include, for example, treatments for cancer and other serious diseases that have demonstrated clear benefits in terms of overall survival.
- The scope of the intervention or technology could potentially be broad, producing health benefits in more than 10% of the country’s population, and there is reasonable certainty about its effectiveness (e.g., good clinical studies showing a magnitude of effect that can be considered clinically relevant across the CI95% range). This category could include, for example, prevention programs, vaccinations, or other public health interventions.
- The technology or intervention is aimed at meeting needs aligned with pre-established Ministry of Health priorities, and there is reasonable certainty about its effectiveness (for example, through good clinical studies showing a magnitude of effect that can be considered clinically relevant throughout the CI95% range). This category could include, for example, interventions for neglected conditions such as Chagas disease.
- There are strong indications, based on the available evidence, that the technology could be as or more effective than current treatments and would represent a lower cost to the health system (cost-saving technology).
- There are strong indications, based on the available evidence, that the technology could yield significant benefits in other socially relevant dimensions (see next chapter on value frameworks). For example, an intervention or technology with a high potential for reducing inequities – for example, by improving access and outcomes in vulnerable populations (e.g., a test for cervical cancer screening in rural populations).

These criteria are proposed as an example of a “filter” or “triage” to assure society that all interventions and technologies that could potentially be “of great value” will be prioritized

in a special way for evaluation and that the decision on their coverage or inclusion in the benefits package will therefore be made within a specific and reasonable period of time. Beyond this example, each jurisdiction will need to set its own criteria to determine when it will consider a technology a high priority for evaluation, and these criteria should be aligned with social values. As previously mentioned, each society determines the elements it considers important differently when assessing the value of a technology, a point that will be addressed in the next chapter on value frameworks.

The main function of a mechanism such as the one described here is to bring peace of mind to the different actors in society, ensuring that all potentially very relevant technologies have been evaluated and a decision about them has been made, or that they are currently being evaluated. Therefore, the fact that a technology is not included in the benefits package or is not covered is a sufficient argument for not providing coverage, since it means it has either already been evaluated and rejected or is being evaluated and must wait for the process to be completed before a coverage decision is made.

As an additional mechanism that could improve perceptions of the legitimacy of the benefits package and coverage decisions, consideration may be given to the option that some technologies that meet these high-priority criteria for evaluation and have already obtained approval by the regulatory agency may be covered as an exception until the evaluation process is completed and a final decision is made on their inclusion in the benefits package. This would be a mechanism similar to that applied in other countries (for example, Germany or even in certain respects, the United Kingdom), allowing certain new technologies to be financed for a limited period of time until a decision has been reached on the matter. With sufficiently strict criteria, not many technologies would be identified as priorities each year (for example, no more than 10 or 15), and with proper coordination with the regulatory agency, it would be easy to identify them early (for example, through horizon scanning) and begin a parallel evaluation to obtain a coverage decision at the same time, or almost the same time, as regulatory approval. This mechanism could reduce judicialization proceedings, since it would give the benefits package even greater legitimacy to act as an exclusion list as well, though withdrawing coverage if the subsequent evaluation does not recommend its incorporation is also more complicated.

Another important element is the proactive search and identification of technologies and interventions by HTA agencies. Which makes it possible to identify promising, potentially effective and cost-effective interventions that are not being widely used or promoted because they do not have a specific sponsor to advocate for their coverage or inclusion in a benefits package; for example, a colon cancer screening program, cardiovascular disease prevention interventions, or guidelines or protocols such as pre-surgical evaluation to avoid unnecessary use of resources. This methodology improves the legitimacy of the benefits package, assuring society that all potentially relevant technologies and interventions have been considered and also serves to align the work of the HTA agency with national health priorities that, especially in middle- and low-income countries, may not be only related to new technologies.

However, beyond the high-priority technologies to be evaluated that could be subject to a different procedure such as the one proposed here, it is common for HTA agencies to have a long list of candidate technologies to be evaluated. This list can be compiled from different sources. The technologies can be identified by the agency itself (for example through horizon scanning); requested by hospitals, provincial or state health secretariats, or

other Ministry of Health entities; or requested for inclusion in coverage or benefits packages by different actors (such as patients and users, industry, or healthcare professionals). For example, several Latin American countries, such as Argentina, Brazil, Mexico, and Uruguay, have open nomination mechanisms for evaluating and including technologies in benefits packages.

As a result of the prioritization process, technologies that do not require evaluation can also be identified, since a decision can be made without the need for an exhaustive evaluation. In other words, the value added that the evaluation could provide in terms of information is so low that it is not worth investing the resources required to conduct it. For example, technologies for which there is no solid evidence of their effectiveness and/or safety can be excluded from coverage without the need for a more thorough evaluation (it would not be necessary to evaluate their cost-effectiveness or other dimensions, for example). As previously mentioned for the Netherlands and countries such as France and Germany, full evaluations are not required for all medicines. If a new drug proves effective but not superior to other, currently available treatments, and the manufacturer agrees to have its price set in reference to these already available alternatives, it would not be necessary to move forward with a full evaluation, and the drug could be included. A different situation may arise if the manufacturer considers its medicine superior to the alternatives and claims the right to set a higher price. In that case, a more complete evaluation (including, for example, a cost-effectiveness analysis) would be necessary to determine whether the additional benefits of this new drug justifies the health system paying a higher price than it currently pays for existing alternatives. Other cases, such as interventions that are clearly cost-saving or more cost-effective than their alternatives, or technologies that are clearly superior and represent a very low budgetary impact compared to their comparators, could also be cases in which a full evaluation is not required for a decision to be made.

1.5. Final remarks

Having explicit transparent mechanisms to prioritize the technologies to be evaluated is one of the principles of HTA good practice (Drummond, 2008; Pichon-Riviere, 2018) and a key contribution to increasing the legitimacy of decisions.

When establishing these mechanisms, each country must determine who may request evaluations or nominate or propose technologies for evaluation; the mechanisms for actively identifying candidate technologies (horizon scanning); the actors who can participate in the process; and the criteria and dimensions to consider in priority setting. Most agencies consider the following criteria: 1) burden of disease of the condition for which the technology is intended; 2) degree of benefit or clinical impact that it would provide; 3) economic impact that inclusion or coverage would produce; 4) existing uncertainty and importance of the information that an evaluation could provide for decision-making.

Implementation of prioritization mechanisms should also involve the establishment of mechanisms for the proactive search for and identification of promising, potentially effective, and cost-effective technologies and interventions (horizon scanning) that are not being widely used or promoted, as they do not have a specific “sponsor.” This active methodology increases the legitimacy of the benefits package and serves to align the work of the HTA agency with national health priorities.

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2. VALUE FRAMEWORKS: DIMENSIONS TO BE CONSIDERED WHEN ASSESSING THE VALUE OF HEALTH TECHNOLOGIES

Although health technology assessment may have different objectives, one of the most important is to maximize the value gained from the use of health resources – that is, to maximize the “value for money” of the investments that the health system must make. This involves comparing the additional value of incorporating a new technology or intervention with the value that could be obtained from the best possible use of those same resources with other technologies or interventions (which in economic terms is known as “opportunity cost”). In other words, including a technology in coverage will produce a certain benefit; if the benefit obtained is greater than the benefit lost (or not obtained) by not having used those resources for other alternatives, then the decision to include the technology was correct.

This approach requires that the benefits of a given technology (the “value” in current terminology) be properly defined and quantified, which involves deciding the criteria and dimensions to consider when assessing its value. This is what is commonly called a “value framework.” This chapter addresses these important aspects.

2.1. Approaches used to assess the value of health technologies

The main aspects whose examination has been proposed to assess the value of health technologies are described below.

Benefits in clinical outcomes

Assessing the clinical benefits of a new technology compared to its relevant alternatives is a central (if not the most important) aspect of value frameworks. Some frameworks consider only clinical benefits, regardless of how they are presented. This is the approach used in France and Germany in evaluating new medicines (Drummond et al., 2014). Based on clinical data, an assessment is made about the “value added” by the new drug compared to existing alternatives (the greater the clinical benefit provided by the drug, the greater its “value”).

The degree to which the new technology provides “value added” is then used to guide price negotiations with manufacturers. The more “innovative” a new technology, the more likely a higher value will be justified, even though in no country is there a one-to-one relationship between the assessment and the final price.

In other contexts, clinical benefits are assessed more systematically by including different dimensions when determining the value of a new technology. One example of this is the value framework used by the American Society of Clinical Oncology (ASCO), which is designed for use in the context of patient-doctor decision-making (Schnipper et al., 2016). In this value framework, the evaluated drugs are assigned a score, taking into account the magnitude of the clinical benefit (progression-free survival or total survival, 0 to 80) and adverse effects or the absence thereof (-20 to +20). Additional points (0 to 30) are also assigned if the drug is to be used in advanced stages of the disease. The objective is for the drug’s total score to be used by doctors, mainly in their conversations with patients, since in the United States, patients may have to make significant outlays to access some of

these drugs. This approach does not include the costs and benefits of these drugs from the general perspective of the health system.

Cost savings

Although most of the benefits of health interventions are related to their impact on health, it is important to mention that some have the effect of reducing costs. The best example of this is certain preventive interventions, such as several immunization programs, which generate savings by reducing cases of the disease (savings that are greater than the costs of the vaccine and the implementation of the vaccination program). This is why in any assessment of health technologies, the cost considered is the net cost of their adoption, which includes both the additional costs and the savings generated by the implementation of the new technology.

Public health benefits

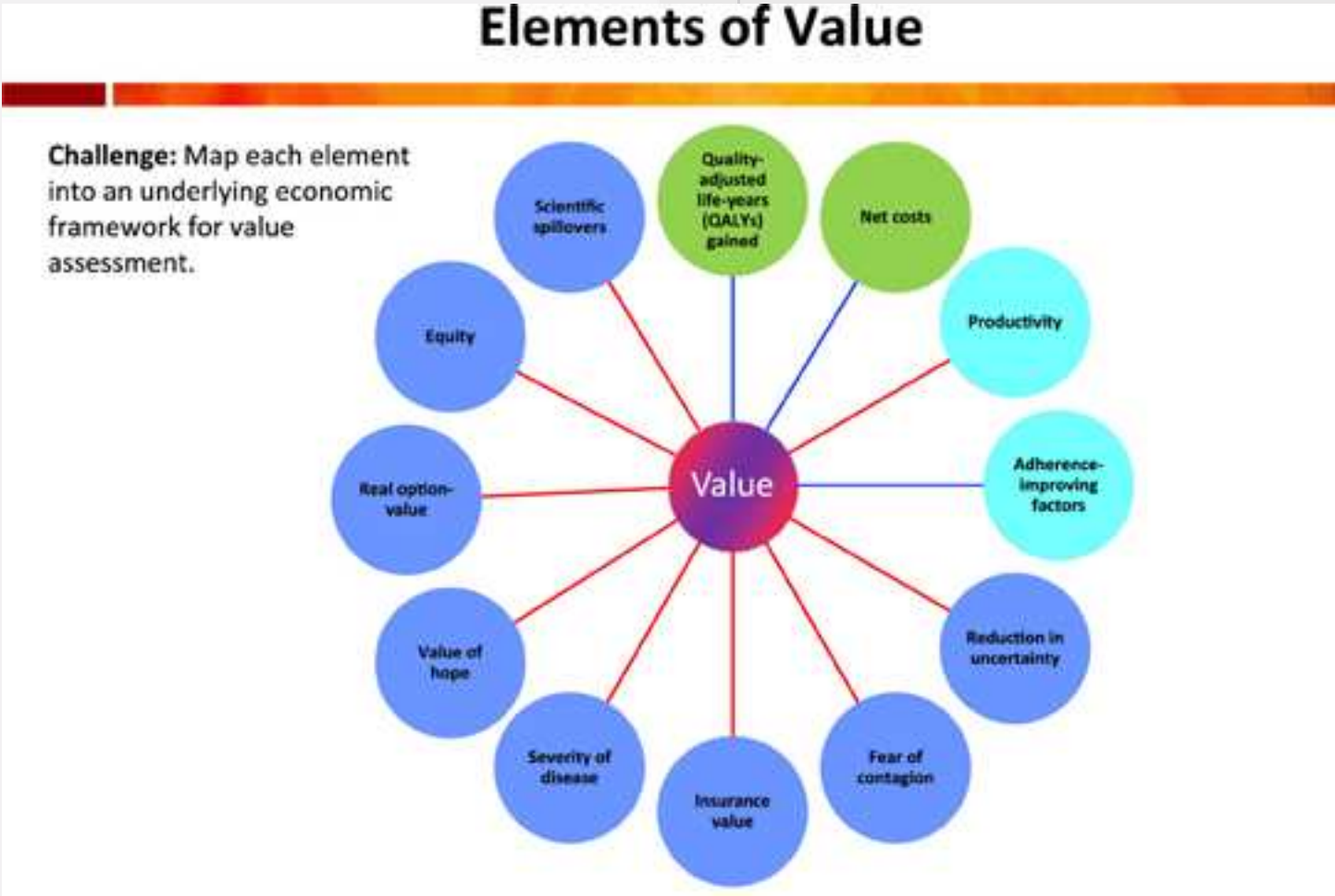
Although the evaluation of clinical benefits is a key aspect in the quantification of value, it has certain limitations. While the evaluation of certain clinical benefits may be useful within a specialty or for a health problem, those same clinical benefits are not necessarily generalizable or extrapolatable between different specialties or health problems. For example, the clinical benefits of a given intervention could be assessed in terms of avoided heart attacks. This measure of clinical benefit could be useful if the object is to compare the value of different interventions in preventing cardiovascular disease; an intervention that manages to prevent more heart attacks would be considered of greater value than one that prevents fewer heart attacks. However, this measure of benefit would not be helpful in measuring the value of cancer treatments. Many policymakers feel that this is a significant limitation, as they expect the evaluation of health technologies to provide information that permits optimization of the use of health resources for the health system as a whole and not just for a certain specialty or therapeutic area. This is why there has always been interest in developing “generic” units of measurement that can capture the health benefit in all areas of health. If this common measure or metric is used by the health system as a whole, then the benefits of different technologies or interventions can be evaluated homogeneously in terms of their incremental cost per unit of incremental benefit obtained.

Much of the literature on health technology assessment has focused on the use of two of these generic measures, the Quality-adjusted Life Year (QALY), which is used primarily in high- and middle-income countries, and the Disability-adjusted Life Year (DALY) developed by the World Bank and the World Health Organization, used primarily in low-income countries (Tan-Torres et al., 2003, Augustovski et al., 2018). Beyond the fact that there are differences in the specific methodology used in the development of these measures, what they have in common is that both are based on combining survival information with quality-of-life data, measured on a scale of 0 to 1 (although in QALY, it is also possible to obtain scores below 0 that mean worse states of health than death, although this aspect is not usually relevant in practice).

The use of QALYs and DALYs in health technology assessment is not without its critics. The main issue is that their construction involves certain questionable assumptions. Moreover, in many cases, it involves extrapolating the benefits of treatments throughout life through mathematical models. Beyond these criticisms, many decision-makers find that estimating the cost per QALY or DALY gained is useful information, since the main alternative, which would be a simple monetary value, also has its limitations.

Furthermore, one of the criticisms of QALYs and DALYs is that they may not capture significant aspects of the value of a technology, which is closely related to the vision and values of decision-makers in different contexts. In England and Wales, NICE’s vision is that the health budget should be executed in a way that maximizes the health gains of the population as a whole; thus, it relies primarily on estimating the incremental cost per QALY gained (although other aspects of technology can also be taken into account, as will be seen further on). However, maximizing the health gains of the population as a whole is not the only possible point of view. An alternative objective is the general welfare of the population, for which a decision-maker could consider other aspects of a technology’s value. Some of these additional aspects and dimensions of value were discussed in the recent ISPOR Special Task Force in Value Assessment (Garrison et al., 2018) (see Figure 2-1).

Figure 2-1 Potential elements of value that could be considered in economic assessments



Note: Green circles: core elements of value. Light blue circles: common but inconsistently used elements of value. Dark blue circles: potential novel elements of value. Blue line: value element included in traditional payer or health plan perspective. Red line: value element also included in societal perspective. Source: Lakdawalla et al. (2018)

In this diagram by Lakdawalla et al., the dimensions in green are those usually included in the evaluation of the value of health technologies and considered key or “core” dimensions: costs and QALYs. Items in light blue are those that are sometimes included in the evaluations, such as the benefits of boosting labor productivity if a technology encourages individuals to remain economically active for longer or return to work earlier; and the benefits of increasing treatment adherence and consequently, the chances that the treatment will be effective (for example, a more comfortable form of administration). Finally, the dimensions in dark blue are rarely considered in evaluations, even though they could constitute an important part of the “value” of the technologies. These dimensions are:

- The value of reducing uncertainty about the diagnosis of a disease
- The value of protection against a contagious disease
- The value of patients being “insured” – that is, of having access to a certain technology, if necessary
- The added value of being a treatment for very serious diseases
- The value of patients’ expectation that they will benefit from a treatment
- The value of patients receiving a treatment that increases survival, enabling the emergence of more effective treatments in the future
- The value of greater equity in access to treatment, especially when a patient is denied it (likely due to a rare disease or the high cost of treatment)
- The value of research externalities that can promote innovation or the development of new treatments

This list helps to illustrate the point that there are many possible dimensions of a technology’s value, although most of them are not routinely considered by all health systems. This list, furthermore, is not exhaustive. For example, some policymakers may also wish to consider the impact on both costs and the quality of life of family members.

Therefore, the first decision is to determine precisely which dimensions will be evaluated and considered to assess the value of technologies and interventions when deciding on their coverage or inclusion in the benefits package. The inclusion or exclusion of certain dimensions is critically dependent on the decision-makers’ values and vision when judging their relevance. It is also necessary to discuss how these dimensions should be measured and combined in the final assessment of a technology’s value.

2.2. Discussion points for Latin American countries and preliminary proposal of general guidelines for the definition of a value framework

In most countries, the benefit of technologies or interventions characterized in clinical terms or measured in QALYs or DALYs is a key component of value frameworks. Its measurement using QALYs or DALYs is the approach embraced by many of the international guidelines for health technology assessment or health economic assessment (Garrison et al., 2018; Wilkinson et al., 2016; Tan-Torres et al., 2003). It will therefore be very useful for any country that is beginning its evaluation process and considering inclusion of the economic dimension in its value framework to develop methodological guidelines for context-specific economic evaluation or at least adopt a previously developed “reference case” considered applicable to the local context.

However, as we have seen, countries or health systems may also wish to consider other dimensions and criteria beyond costs and QALYs/DALYs when assessing the value of technologies. Selection of the relevant criteria on which decisions will be based is one of the critical points in building transparency into the decision-making process. These criteria should reflect the overall objectives of the health system (usually defined as the maximization of population health, equal distribution of health, and financial protection), and other underlying social values such as equity, solidarity, and access to quality health care (Oortwijn 2019). Once the general objectives and values of the health system have been defined, they can be specified in a series of decision-making criteria that will comprise the value framework. This process should involve appropriate participation by the different actors to ensure that the value framework that is eventually defined effectively reflects social values.

Not all countries have gone through the process of exploring and explicitly defining a value framework. In fact, most HTA agencies in Latin America operate without a formal value framework. Nonetheless, these same agencies conduct technology assessments on a daily basis and make decisions or issue recommendations. These assessments are based on the dimensions and criteria they consider important and a judgment is made about how the technology performs in the dimensions evaluated. When issuing a recommendation, the agencies must consider the importance assigned to each criterion or dimension, based on what decision-makers consider the health system’s objectives, as well as other social values. In other words, there is always a “value framework” that guides the HTA process, even if it is merely implicit. For example, if in making decisions, a country assesses and considers the effectiveness, cost-effectiveness, and budgetary impact of technologies, as well as the severity of the condition they are designed to treat, it means that these are the criteria and dimensions considered important when deciding on coverage. A judgment should also be made about how the technology performs in each dimension evaluated. For example, it must be determined whether the clinical benefit is relevant, cost-effective, or the budgetary impact is acceptable. Hence, there must be a rule, even if implicit and different for each decision-maker, that guides this determination. Finally, it is also necessary to have a position on the relative importance of each dimension or criterion, and it must be judged how to balance the performance among different dimensions and integrated them into a final assessment.

For example, a technology could be effective and target a serious disease but have a high budgetary impact or not be very cost-effective. What would be the recommendation in this case? (See Chapter 4). When countries conduct assessments and make recommendations, there is always a value framework, even if implicit, often without decision-makers being fully aware of it. Nonetheless, the fact that it is not explicit has a number of implications. There is a risk that different decision-makers will use different value frameworks, that two similar technologies will be assessed differently, or that different decisions will be made for the same technology depending on when or where they are made. At the same time, there is no guarantee that the value framework in use adequately reflects what society considers important.

Lack of an explicit value framework implies a lack of consistency and predictability and, above all, jeopardizes the transparency and legitimacy of decisions. An explicit value framework is a guide that enables those conducting the HTA to know which dimensions to evaluate; those responsible for issuing the recommendations to know how to assess their value; and patients, users, and manufacturers of the technologies and all stakeholders to have clear

rules governing participation.

Defining a value framework implies determining which elements, domains, criteria, or dimensions will be considered when assessing the value of health technologies. As indicated above, the Special Task Force of ISPOR on Value Assessment Frameworks states that the evaluation of cost-effectiveness (with outcomes measured in QALYs) is the key element, although it mentions many other dimensions that could also be considered.

The 2018 HTAi Policy Forum of Latin America (HTA International Society) suggests that the essential elements to include in value frameworks are (Pichon-Riviere 2019):

- Effectiveness (magnitude and relevance of clinical benefit)
- Security
- Quality of evidence
- Burden of disease
- Severity of the disease
- Budgetary impact
- Cost-effectiveness

The Forum also mentions the following criteria as non-essential, but nevertheless high priority:

- Patient technology preferences
- Accessibility for patients
- Costs to patients and their family
- Impact on equity
- Impact on public health

Some countries and HTA agencies have defined the value framework they will use when assessing technologies. For example, CONETEC (National Commission for Technology Evaluation of Argentina) has established a group of dimensions/criteria in a value framework for new technology assessment that includes the following dimensions (CONETEC 2019):

- Quality of evidence
- Magnitude of clinical benefit
- Economic impact (budgetary impact and cost-effectiveness)
- Impact on equity
- Impact on public health

As can be seen, these groups of criteria largely overlap, since in order to obtain a reliable estimate of cost-effectiveness, the quality and relevance of the clinical evidence (such as efficacy-effectiveness, safety, quality of evidence) must be considered before including it in the estimation of QALYs gained and the uncertainty surrounding that estimate.

For Latin American countries that have not yet completed formal definition of their value framework, there are strong arguments to recommend that, until the framework is defined, decisions about the allocation of health resources should consider the following criteria:

- Magnitude and relevance of clinical benefit (Effectiveness)
- Quality of evidence

- Cost-effectiveness
- Budgetary impact
- Impact on equity
- Impact on public health

The following criteria could also be considered to be among the essential criteria or other high-priority criteria:

- Burden of disease
- Severity of the disease
- Patient technology preferences
- Accessibility for patients
- Costs to patients and their family

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3.DETERMINING THE OPPORTUNITY COST IN HEALTH

In order to reach a decision on coverage, inclusion in the benefits package, reimbursement, or price of a new technology, a decision rule is needed. In the literature, most of the discussion on decision-making rules took place within the context of the cost-effectiveness of interventions, especially the cost-effectiveness threshold. However, a decision rule is also necessary even if only clinical benefits are being considered. For example, in France, new medicines are assigned a category on the Added Medical Services Rendered (ASRM) scale ranging from 1 to 5. To be assigned an international price not limited by reductions based on local reference prices, the decision rule requires that the drug have a score of 1, 2, or 3 on this scale (Drummond et al., 2014). These decision rules allow health systems to determine whether the technologies they are assessing meet certain predefined requirements and thereby assist the decision-making process.

In the context of health technology assessments that include an economic evaluation, the discussion revolves around how this should be the decision rule for determining whether a given incremental cost-effectiveness ratio (ICER) is considered acceptable in the jurisdiction in question. The World Health Organization’s initiative on Generalized Cost-Effectiveness (Sachs, 2001), suggested at the time that countries could consider an intervention whose ICER was less than 1 GDP per capita per DALY as very likely cost-effective, or below 3 GDP per capita per DALY as likely cost-effective. Although some low- and middle-income countries continue to use the benchmark of a cost-effectiveness ratio of 1 GDP per capita when assessing the inclusion of new technologies, WHO no longer makes this recommendation and most Latin American countries do not have an explicit cost-effectiveness threshold.

3.1. Estimating the threshold

While many countries in the region have some decision rule, reference, or threshold for determining the cost-effectiveness of technologies, this rule is usually implicit. It is argued that making it explicit would reduce decision-makers’ flexibility and could lead to technology manufacturers raising their prices up to the threshold level, resulting in less cost-effective technologies (Wang et al., 2018). In contrast, the argument for making the decision rule or threshold explicit is that it makes the decision-making process more transparent and promotes greater consistency in decisions. The sections below describe various methodologies for estimating the threshold.

Threshold estimation based on opportunity cost

This is the approach preferred by most health economists. In this case, the opportunity cost threshold represents the shadow price in the current health budget constraint. In other words, the threshold represents the lost value of the health benefits of the technologies that will have to be displaced or cannot be covered to permit the introduction of the new technology.

For example, given a fixed health budget, including and covering new expensive cancer treatments will mean that the health system will not be able to provide some existing services or technologies. If the health benefits obtained with the new treatments are greater than

the lost benefits of the services that will be displaced, it will not be a problem, since the net gain in health will be positive (the benefits gained are greater than the benefits lost). If they are not and the benefits provided by the new treatments fail to offset the benefits that the system fails to obtain, then the net result will be less health for the system as a whole. Simply put, this opportunity cost threshold represents the cost-effectiveness of the services or technologies that will be displaced in the margin to introduce new technologies. If new technologies are above this threshold, the system as a whole will end up losing health.

To put it in numbers: suppose the opportunity cost in a given country has been estimated at \$1,000 per quality-adjusted life year (QALY). If this country includes a technology whose ICER is US\$ 500 per QALY in its coverage, the net result will be positive, since it can be estimated that the technologies that cannot be financed due to the inclusion of this new technology would have a less favorable cost-effectiveness, as defined by the opportunity cost threshold (US\$ 1,000 per QALY). On the other hand, if this country includes a technology with an ICER above the threshold (for example US\$ 2,000 per QALY), it would be losing health, since the opportunity cost value precisely indicates that there could be more cost-effective technologies that cannot be covered.

Even if a country decides not to base its decision rule on the opportunity cost, it is important to know what that value is, since it will enable it to know how much health is being lost or gained with each decision (Sculpher et al., 2017). Further on, we will see how the opportunity cost in health can be estimated and present estimates for the countries of the region.

Threshold estimation based on current practices of decision-makers

Another approach to determining the threshold is to review previous coverage decisions and estimate the threshold that was implicit in those decisions. This was partly the approach used in the United Kingdom to reach the threshold used today by NICE. In a review of NICE’s first decisions (Devlin and Parkin, 2004), it was observed that the probability that an intervention would be rejected increased substantially when the incremental cost-effectiveness ratio of the intervention was greater than £20,000 per QALY. Based on this investigation, NICE, which up to that point had had no explicit threshold, determined that it would use a threshold of £20,000 per QALY, which could be as high as £30,000 under special conditions.

This same approach was recently used in Japan, which included the requirement of cost-effectiveness evidence as part of its drug pricing policy. While likely to lead to a higher comfort level for decision-makers, this approach is based on decisions made in the past. If the decisions were resulting in a misallocation of resources since the built-in interventions produced less health than the displaced ones, basing a threshold on these decisions would only perpetuate the problem.

Threshold estimation based on health spending aspirations

Although not explicit at the time, WHO’s original recommendation of a threshold of 1-3 GDP per capita was largely based on the level of anticipated health expenditure. While there is nothing wrong with aspiring to increase the health budget, the principle of opportunity cost implies that if the cost-effectiveness threshold used to decide on the introduction of new technologies is higher than the cost-effectiveness of technologies that could be displaced, then health will be lost unless the health budget is increased. Therefore, from the standpoint of opportunity cost, a threshold cannot be determined without taking the health budget into account (Culyer, 2017). Thus, a decision to use a threshold based on what is aspired to or

believed to be correct should be accompanied by a discussion on whether this implies that the health budget should be increased. In Latin America, we can find examples of what could be considered aspirational thresholds. For several years, Mexico recommended a threshold of 1 GDP per capita for interventions that were to be included in the “Basic Table,” and the methodological guide for conducting economic assessments in Chile suggests a threshold of 1 GDP per capita for an intervention to be considered cost-effective (Augustovski et al., 2010).

Threshold estimation based on social preferences

From this perspective, the information to determine the threshold could be obtained from surveys of the population that ask about the willingness to pay for a year of life or QALY. This was attempted in Europe, but finding the appropriate way to ask the questions proved difficult. A review of published studies (Mason et al., 2008) found that the number individuals willing to pay for a QALY varies widely depending on the context. Beyond this, it was concluded that such estimates could be useful in informing the debate about cost-effectiveness thresholds.

However, as we previously noted in regard to determining a threshold based on spending aspirations, it would not be reasonable to increase the threshold on the basis of social preferences without an increase in the health budget. Therefore, if these surveys on the willingness to pay for QALY/DALY can serve any purpose, it is to provide evidence about society’s eventual support for increasing the health budget.

3.2. Estimating the opportunity cost

As previously mentioned, regardless of the approach used to determine the decision rule or threshold in a given country, it is important to know the opportunity cost. In the United Kingdom, the debate surrounding the threshold used by NICE led to studies to estimate the opportunity cost, since they provide an empirical basis for setting the threshold. This research involved an econometric analysis that took health expenditure and its associated health outcomes (reduction in mortality) in different jurisdictions into account. The most important constraint was the lack of some basic data (for example, the studies used available mortality data but had to make assumptions about the effect on quality of life) and the lack of information on interventions shifted in the margin in different health areas with different levels of expenditure. Although there is no consensus on the best approach to estimating opportunity cost, several studies in the United Kingdom and other countries estimated opportunity cost values consistently lower than the thresholds currently used. In the United Kingdom, the estimate was approximately £13,000 (Claxton et al., 2015). In Spain, it was estimated at €22,000-€25,000 per QALY (Vallejo-Torres et al., 2016).

In Sweden, using information from the various municipalities, a value of €39,000 per year of life gained was estimated (Siverskog et al., 2019). In Australia, this value was estimated at A\$28,000 (Edney 2018). Finally, a recent study in the United Kingdom (Lomas et al., 2019) estimated a marginal productivity value for the National Health System of £5,000-£15,000 for the period 2003-2012, significantly lower than the threshold used by NICE during the same period.

Threshold estimation methodologies have recently been developed and have been extended or applied in several countries. The research group at York University in the United Kingdom conducted research that estimated opportunity cost thresholds for different countries,

including Canada, India, and countries in Latin America (Claxton et al., 2015; Woods et al., 2015; Ochalek et al., 2015; Ochalek et al., 2018; Ochalek et al., 2019). The research team at the Institute of Clinical and Health Effectiveness of Argentina (IECS) developed a methodology based on per capita health expenditure and life expectancy that it used to estimate cost-effectiveness thresholds for 176 countries (Pichon-Riviere et al., 2017).

As we will see further on, a large part of the opportunity cost estimates made to date have yielded values lower than the thresholds used in practice. This implies that in many cases, health systems may be losing more health benefits than they actually gain by introducing certain health technologies.

3.3. Discussion points for Latin American countries and preliminary proposal of opportunity cost values for countries without their own estimates

Estimating opportunity cost can be challenging. On the one hand, there is no unanimously accepted methodology. On the other hand, most of the existing methodologies were developed in high-income countries and usually require a large volume of high-quality information from the health system, which is not always available in low- and middle-income countries. This section offers guidance for enabling countries to obtain a preliminary first estimate, or guide, on what the opportunity cost value in their health systems might be.

Table 3-1 presents the main results of a series of opportunity cost estimates made with different methodologies in a wide range of countries, including high-, low-, and middle-income countries, some of them in Latin America. To improve the comparability of these values among countries, the opportunity cost is also presented as a fraction of GDP per capita and as an equivalent in health expenditure per capita.

Table 3-1 Estimates of opportunity cost in different countries: sources, ranges, and estimates in units of GDP and health expenditure per capita.

| Citation | Country | Year of study | Benefit measurement unit | Currency reported in the study | Reported opportunity cost (currency reported in the study) | | | Country data (currency reported in the study) | | Opportunity cost in relation to: | |
|------------------------|--------------|---------------|--------------------------|--------------------------------|--|-------------|-------------|---|-------------------------------|----------------------------------|-------------------------------|
| | | | | | Central estimate | Lower Limit | Upper Limit | GDP per capita | Per capita health expenditure | GDP per capita | Per capita health expenditure |
| Lomas 2018 | Canada | 2013 | DALY | CAD | 50,000 | 20,000 | 100,000 | 54,087 | 5,481 | 0.92 | 9.12 |
| Lomas 2019 | UK | 2012 | QALY | GBP | 14,411 | 11,182 | 19,861 | 26,935 | 2,246 | 0.54 | 6.42 |
| Ochalek 2019 | India | 2015 | DALY | INR | 18,196 | 14,116 | 22,275 | 105,117 | 3,782 | 0.17 | 4.81 |
| Edney 2018 | Australia | 2012 | QALY | AUS | 28,033 | 20,758 | 37,667 | 65,958 | 5,731 | 0.43 | 4.89 |
| Claxton 2015 | UK | 2008 | QALY | GBP | 12,936 | 2,018 | 29,314 | 23,611 | 1,814 | 0.55 | 7.13 |
| Vallejo-Torres 2017 | Spain | 2012 | QALY | Euros | 23,500 | 22,000 | 25,000 | 22,231 | 2,018 | 1.06 | 11.65 |
| Woods 2016*+ | Brazil | 2013 | DALY | USD | 4,969 | 2,393 | 7,544 | 12,300 | 1,259 | 0.4 | 3.95 |
| | Chile | 2013 | DALY | USD | 7,166 | 4,896 | 9,436 | 15,843 | 1,179 | 0.45 | 6.08 |
| | Colombia | 2013 | DALY | USD | 3,444 | 1,370 | 5,518 | 8,213 | 477 | 0.42 | 7.22 |
| | Mexico | 2013 | DALY | USD | 4,580 | 2,410 | 6,749 | 10,725 | 623 | 0.43 | 7.35 |
| | Peru | 2013 | DALY | USD | 2,764 | 1,144 | 4,383 | 6,757 | 333 | 0.41 | 8.30 |
| | Uruguay | 2013 | DALY | USD | 7,348 | 4,548 | 10,147 | 16,974 | 1,497 | 0.43 | 4.91 |
| Ochalek 2018#+ | Argentina | 2015 | DALY | USD | 6,203 | 4,936 | 7,469 | 13,789 | 1,206 | 0.45 | 5.14 |
| | Brazil | 2015 | DALY | USD | 7,683 | 6,048 | 9,318 | 8,814 | 1,011 | 0.87 | 7.60 |
| | Colombia | 2015 | DALY | USD | 9,263 | 7,067 | 11,459 | 6,176 | 372 | 1.5 | 24.9 |
| | Mexico | 2016 | DALY | USD | 7,227 | 5,723 | 8,730 | 9,606 | 543 | 0.75 | 13.31 |
| | Peru | 2017 | DALY | USD | 5,184 | 3,836 | 6,531 | 6,229 | 319 | 0.83 | 16.25 |
| Pichon-Riviere 2019 &+ | Argentina | 2016 | QALY | USD | 14,622 | 7,494 | 27,259 | 12,790 | 965 | 1.14 | 15.15 |
| | Brazil | 2017 | QALY | USD | 14,646 | 7,586 | 26,894 | 8,713 | 1,026 | 1.68 | 14.28 |
| | Chile | 2018 | QALY | USD | 14,288 | 8,128 | 25,197 | 13,748 | 1,173 | 1.04 | 12.19 |
| | Colombia | 2019 | QALY | USD | 5,661 | 2,878 | 10,680 | 5,871 | 347 | 0.96 | 16.31 |
| | Mexico | 2020 | QALY | USD | 6,440 | 3,351 | 11,749 | 8,740 | 478 | 0.74 | 13.47 |
| | Peru | 2021 | QALY | USD | 4,818 | 2,474 | 8,961 | 6,205 | 319 | 0.78 | 15.09 |
| | Uruguay | 2022 | QALY | USD | 13,719 | 7,955 | 23,558 | 15,387 | 1,394 | 0.89 | 9.84 |
| Baal 2018 | Netherlands | 2015 | QALY | Euros | 41,000 | 25,900 | 110,400 | 40,732 | 4,234 | 1.01 | 9.68 |
| Siverskog 2019 | Sweden | 2016 | QALY | Euros | 45,394 | 24,738 | 275,078 | 46,621 | 5,098 | 0.97 | 8.90 |
| Edoka 2020# | South Africa | 2015 | DALY | USD | 3,296 | 3,015 | 3,577 | 5,700 | 471 | 0.58 | 7.00 |

* The mean estimate of the threshold is calculated as the average between the upper and lower limits

The mean estimate of the threshold is calculated as the average between the upper and lower values obtained from the different reported methods

+ Results are shown for a selected group of Latin American countries

& Not strictly an opportunity cost estimate

In most cases, the opportunity cost estimate was below 14 health expenditures per capita. In terms of GDP, in a third of the cases the estimate was below 0.5 GDP per DALY or QALY, and in almost 80% of the cases it was less than 1 GDP per capita. Less than 4% of the countries had estimates of their opportunity cost above 1.5 GDP per QALY or DALY, and in all cases, they were below 2 GDP per capita.

Some of these estimates are based on important methodological assumptions, such as extrapolation of the elasticity of health expenditure from places where it was measured (such as the United Kingdom) to others where it was not directly measured (such as Brazil or Chile). Moreover, in some cases, estimates are shown for several Latin American countries but conducted with the same methodology (Woods et al., 2016; Ochalek et al., 2018; Pichon-Riviere et al., 2017). These are significant limitations when analyzing this information, but to date, they are virtually the only opportunity cost estimates available.

What is the best estimate of the opportunity cost in health that can be made in the absence of specific data for a particular health system and country?

Based on the results obtained in several countries, it seems reasonable, in the absence of specific and precise data by country, to estimate that the opportunity cost can probably be found in a value ranging from 7 to 14 health expenditures per capita (central estimate of 10.5 health expenditures) or, translated into the GDP of the countries, from 0.5 to 1 GDP (central estimate of 0.75 GDP). In the case of the countries presented in Table 3-1, the cost-opportunity estimates were within or below this range in almost 80% of them.

Because there is no consensus or clear recommendation on the advisability of extrapolating opportunity cost data between countries based on GDP per capita or health expenditure per capita, these results were extrapolated to Latin American countries using the following equation, which considers both factors:

$$OC_{US\$} = \frac{HEpc \cdot R_{HEpc} + GDPpc \cdot R_{GDPpc}}{2}$$

where OC_{US\$} is the opportunity cost estimate; HEpc is the per capita health expenditure, and GDPpc is the value of GPD per capita of the country or health system for which the opportunity cost is to be estimated; R_{HEpc} is the multiple of health expenditures per capita; and R_{GDPpc} is the multiple of GDPs per capita used as a reference to estimate the opportunity cost.

Table 3-2 shows the values, in current US\$ 2016 and in fractions of GDP per capita, of the opportunity cost estimates for several Latin American countries, according to the methodology described.

Table 3-2 Estimates of the opportunity cost in different Latin American countries, extrapolated from the results obtained in international studies (US\$ 2016 and, in parentheses, fraction of GDP 2016)

| Country | Central Estimate | Lower Limit | Upper Limit |
|-------------|------------------|-------------|--------------|
| Argentina | 11,196 (0.9) | 7,464 (0.6) | 14,927 (1.2) |
| Belize | 3,433 (0.7) | 2,289 (0.5) | 4,577 (0.9) |
| Bolivia | 2,272 (0.7) | 1,515 (0.5) | 3,029 (1.0) |
| Brazil | 8,601 (1.0) | 5,734 (0.7) | 11,468 (1.3) |
| Chile | 11,406 (0.8) | 7,604 (0.6) | 15,208 (1.1) |
| Colombia | 3,989 (0.7) | 2,659 (0.5) | 5,318 (0.9) |
| Costa Rica | 9,041 (0.8) | 6,028 (0.5) | 12,055 (1.0) |
| Cuba | 8,119 (1.0) | 5,412 (0.7) | 10,825 (1.3) |
| Ecuador | 4,923 (0.8) | 3,282 (0.5) | 6,564 (1.1) |
| El Salvador | 2,968 (0.8) | 1,979 (0.5) | 3,957 (1.0) |
| Guatemala | 2,820 (0.7) | 1,880 (0.5) | 3,760 (0.9) |
| Honduras | 1,920 (0.8) | 1,280 (0.6) | 2,560 (1.1) |
| Mexico | 5,702 (0.7) | 3,801 (0.4) | 7,602 (0.9) |
| Nicaragua | 1,778 (0.8) | 1,185 (0.6) | 2,371 (1.1) |
| Panama | 10,847 (0.8) | 7,231 (0.5) | 14,463 (1.0) |
| Paraguay | 3,713 (0.7) | 2,475 (0.5) | 4,950 (0.9) |
| Peru | 3,988 (0.6) | 2,659 (0.4) | 5,318 (0.9) |
| Uruguay | 13,010 (0.8) | 8,674 (0.6) | 17,347 (1.1) |

Note: For the opportunity cost estimate (OCUS\$) the values corresponding to GDP and health expenditure (GDPpc and RGDPpc) for the last available year (2016) were obtained from the World Bank (<https://data.worldbank.org>). In the case of Argentina, the health expenditure values correspond to local estimates made by the Ministry of Finance (*). For all estimates, the RHEpc values of 10.5, 7, and 14 and RGDPpc values of 0.75, 0.50, and 1.00 for the central estimates, lower limit and upper limit, respectively, were used

(*) Secretariat of Economic Policy, Ministry of Finance. Consolidated Expenditure 2004-2015. Available at: https://www.argentina.gob.ar/sites/default/files/gto_publico_consolidado_2004-2015_corrientes.xlsx. Accessed July 2019.

These preliminary estimates can serve as a guide for countries that do not yet have their own estimates of the opportunity cost threshold in their jurisdictions. As previously mentioned, these thresholds allow health systems to determine whether a given intervention is cost-effective in terms of opportunity cost. For example, taking these proposed values as a reference, a technology with an ICER of US\$ 6,000 per QALY would be cost-effective in Chile, as it is clearly below the estimated opportunity cost value for the country (US\$ 11,000). On the other hand, an intervention with an ICER of US\$ 9,000 per QALY would not be cost-effective in Mexico from the standpoint of its opportunity cost, and therefore its coverage would imply a net loss of health benefits.

If cost-effectiveness and maximization of health benefits were the only criteria to be used to allocate the necessary resources, it would be easy to create a decision rule based only on the opportunity cost threshold: if the ICER of a certain technology or intervention is below the threshold, it can be included in the coverage or benefits package; if the ICER is above the threshold, it should not be. However, as mentioned earlier, health systems also tend to take other dimensions such as budgetary impact or social valuation into account, as seen in the next chapter. Finally, these opportunity cost estimates are made at the country level and could therefore be less representative or applicable in countries with fragmented health systems, where the opportunity cost is not homogeneous throughout the country and may vary in the different subsectors (see Chapter 7).

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4.DECISION-MAKING THRESHOLDS AND MODIFIERS

Even in countries with an explicit decision rule, most decision-makers prefer to have a certain degree of freedom or discretion to exercise their judgment. Therefore, in many countries with an explicit cost-effectiveness threshold, it is presented as a range and not a single fixed value. In other cases, the possibility is considered that there are specific reasons for it to be more flexible and not adhere to that single threshold. Some countries, such as the United Kingdom, have different thresholds for different types of technologies or patient populations. We will call these aspects “modifiers” that can affect the decision-making process under certain circumstances. These potential modifiers are the main focus of this chapter.

4.1. Modifiers to the decision in the deliberative process

The term “modifiers” is used to identify the reasons for allowing alterations in the application of the “general” decision rule, but in a clear, transparent manner prior to the particular decision. For example, in Scotland, the Scottish Medicines Commission (SMC) identifies the following “modifiers” (Scottish Medicines Consortium 2019):

1. Evidence of a substantial increase in life expectancy (with sufficient quality of life to make additional survival desirable). A substantial increase in life expectancy is considered to be a three-month increase in median survival, beyond which the SMC evaluates each situation in a particular way depending on the clinical context;
2. Evidence of substantial improvement in quality of life (regardless of an increase in survival);
3. Evidence that a subgroup of patients can obtain an extra or specific benefit and that the drug in question can, in practice, specifically target this subgroup;
4. Absence of another therapeutic alternative of proven efficacy provided by the National Health System for the pathology in question;
5. Possibility of serving as a bridge to another definitive therapy (e.g., bone marrow transplantation or curative surgery) in a defined proportion of patients;
6. Emergence of a drug approved for a specific indication as an alternative to one not approved for that indication but used in clinical practice in Scotland’s health system as the only therapeutic option for it. Some examples are the injection of caffeine in the treatment of apnea of prematurity or betaine as adjuvant treating in homocystinuria.

Many of the modifiers used in different parts of the world are related to the dimensions of value mentioned in Chapter 2. For example: the treatment targets a very serious or life-threatening condition; the treatment is for a condition that does not have an effective therapy (so it may be fair to offer some therapeutic alternative); the treatment represents a bridge until patients can obtain a more effective therapy; the treatment represents a major innovation, offering a substantial change in life expectancy or quality of life; if not covered, the treatment may put the patient or his family at financial risk.

The list of modifiers is determined by the decision-makers’ vision in each context. Surveys were conducted in some jurisdictions to assess the degree of support for the use of certain

modifiers (for example, Rowen et al., 2015 and Linley & Hughes, 2012 in the United Kingdom). Modifiers are normally applied within the framework of the deliberative decision-making process, which usually is essentially the discussion that takes place around clinical and cost-effectiveness evidence.

4.2. Modifiers reflected in the use of “differential” thresholds

One way in which modifiers are used is by determining different decision-making thresholds for different situations. In 2009, NICE determined that for treatments considered “end-of-life” that prolonged survival by at least three months in patients with less than two years of life expectancy, the committee could value earned QALYs higher than in other circumstances (NICE, 2009).

Since implementation of this “end-of-life” guide in the United Kingdom, the committee rated “end-of-life” QALYs up to 2.5 times higher than the usual QALYs. As a result, this is now reflected in a cost-effectiveness threshold for including these treatments that can reach £50,000 per QALY, rather than the usual threshold of £20,000.

Another situation in which some health systems may consider a different threshold is in the case of highly specialized treatments. These are often technologies for serious diseases or diseases with a risk of death for which there is no specific treatment, mostly ultra-orphan drugs for ultra-rare diseases.

In the United Kingdom, NICE, together with the National Health System, conducted a survey of the population on different proposals to modify the way in which these highly specialized technologies were evaluated and funded. The original proposal was to increase the threshold for these technologies to a maximum of £100,000 per QALY (five times the usual threshold in the United Kingdom). After the survey, the proposal was accepted and the standard modified to allow the use of a cost-effectiveness threshold of £100,000 per QALY for these technologies, allowing it to be increased to a maximum of £300,000 per QALY depending on the total QALYs the technology can provide; this maximum threshold may be considered in exceptional cases where a technology can provide a maximum level of additional survival (30 QALYs or more) (NICE, 2017).

Although, as we have seen, there are health systems that accept the use of modifiers in certain circumstances, decision-makers must be aware that the use of cost-effectiveness thresholds that are higher than the opportunity cost conflicts with the objective of maximizing population health. For example, if we assume that the United Kingdom’s usual threshold (£20,000 per QALY) correctly reflects the opportunity cost, then gaining a QALY by funding an ultra-specialized technology at a cost of £300,000 per QALY would involve the loss of 15 QALYs. This is because funding the ultra-specialized technology would imply shifting resources from other interventions that could have yielded a greater benefit. The net result of financing this technology will be a loss of 14 QALYs (for every QALY gained by this technology, 15 QALYs are lost in the rest of the total population). The loss of QALYs could be even greater if the true opportunity cost in the United Kingdom is below the usual cost-effectiveness threshold of £20,000, as suggested by the Claxton et al. study in 2015.

Notwithstanding, it is common to find that the decision-making thresholds used by countries do not match their opportunity cost values. No studies, in either the United Kingdom or other countries, estimated values consistently lower than the opportunity cost at decision-

making thresholds. In the United Kingdom, the opportunity cost estimate was approximately £13,000 (Claxton et al., 2015), a value lower than the £20,000 decision-making threshold. In Spain, an opportunity cost of €22,000-€25,000 per QALY (Vallejo-Torres et al., 2016) was estimated, also lower than the threshold of €30,000 usually used as a reference. In Sweden, using information from the various municipalities, a value of €39,000 per year of life gained was estimated (Siverskog et al., 2019), when the threshold commonly used in that country is €48,000. In Australia, a value of A\$28,000 was estimated (Edney 2018), a substantial difference from the threshold of A\$50,000 usually taken as a reference. Finally, a recent study in the United Kingdom (Lomas et al., 2019) estimated a marginal productivity value in the National Health System of £5,000-£15,000 for the period 2003-2012, which is also significantly lower than the threshold used by NICE in the same period. These differences show that other aspects are allowing the decision rule to be modified.

4.3. Discussion points for Latin American countries wishing to establish a decision-making rule for the inclusion of technologies

Countries in their early stages of formalizing the use of health technology assessment should consider a number of aspects when discussing how economic evidence will be taken into account in the decision whether to cover or include technologies in benefits packages. The following are some of the questions that may arise during this process:

(a) Decision-makers will need to discuss the characteristics that a decision rule might have in their jurisdictions and the extent to which it should be transparent and explicit. If the incremental cost-effectiveness of the technologies is to be used for decision-making, there must be an explicit definition of the threshold and the elements on which it is based. If the threshold is not defined in relation to the opportunity cost, the rationale for this deviation and its potential consequences in terms of lost health should be discussed.

(b) Decision-makers should discuss whether, given the chosen decision rule, modifiers may be considered that could alter its application in special circumstances.

(c) If there are modifiers considered relevant, their nature must be defined.

(d) The best way to apply these modifiers may be in a deliberative decision-making process, assigning a different weight to the QALY based on the situation or, what is equivalent and perhaps clearer, using different thresholds for different technologies or groups of diseases.

Potential implications of the use of modifiers in decision-making

As mentioned, if the sole objective of a health system were to maximize the health of the population, it would only need to consider the cost-effectiveness of the interventions, and opportunity cost would be the only relevant threshold. However, the decision to include a technology whose incremental cost-effectiveness ratio (ICER) is above the opportunity cost may be justified for certain technologies with attributes valued by the health system or society (such as reducing inequity or benefitting those who are worse off). As these decisions imply diminishing the health of the population as a whole to the benefit of a particular group or groups, the limits within which these other dimensions can be considered should be discussed or defined.

Decision rules are precisely the tool for specifying the modifiers and the limits within which

they can be applied. In which cases will it be valid for the system to consider acceptable a decision that implies a net loss of overall health? What characteristics should the technologies or clinical circumstances that could justify it have? What are the relevant modifiers for society and how can they be applied? What margin is society willing to give decision-makers to deviate from what would be the most efficient allocation of resources?

The next section presents a model that could be used as a guide for countries that are in the process of discussing these decision rules.

4.4. Example of a decision rule and modifiers

As discussed above, countries that decide to allow modifiers need clear rules that define under what circumstances and within what limits they may be applied.

In this regard, an example of a decision rule and the application of modifiers are presented below. The example is not prescriptive, of course. It is intended to serve as a reference and guide when discussing a decision rule to apply with respect to economic evidence, or how different modifiers could be included.

This decision rule is based on (or anchored in) opportunity cost, in the sense that a given technology can only be considered cost-effective only if its ICER is similar to or below the opportunity cost threshold. However, it provides for the existence of situations in which the use of modifiers could be justified, which allows for a shift away from the opportunity cost in some cases. This implies that there will be different thresholds (expressed as multiples of opportunity cost per QALY) in four categories in which we will divide health interventions and technologies. Here we observe a possible categorization of different situations and modifiers.

- A. Health technologies or interventions that are cost-saving or clearly cost-effective according to the local opportunity cost threshold.
- B. Health technologies or interventions that perform well in dimensions considered relevant according to the local value framework and that could be covered despite the absence of an optimal cost-effectiveness profile.
- C. Special cases of effective health technologies or interventions for serious life-threatening diseases, which may not be cost-effective according to the local opportunity cost threshold.
- D. Special cases of effective health technologies or interventions for serious ultra-rare diseases that seriously threaten life and may not be cost-effective according to the local opportunity cost threshold.

Figure 4-1 graphically shows the four threshold levels on the cost-effectiveness plane for each of the categories mentioned. As can be seen, category A technologies are virtually the only ones with an ICER clearly below the opportunity cost threshold and therefore the only ones that can be considered cost-effective from this standpoint. The technologies in the other three categories (B, C, and D) have an ICER equal to or greater than the opportunity cost value of the health system, so their coverage or inclusion in the benefits package could imply a net loss of health benefits. It is important to note that the further technologies are from the opportunity cost threshold (D rather than C, and C rather than B), the greater the overall loss of health benefits to the benefit of some favored groups (or loss of efficiency). In the decision rule we indicate here, these lost benefits could be justified in certain cases

by gains in other dimensions considered important, as discussed below.

Figure 4-1 Different cost-effectiveness thresholds of decision making and their relationship with the opportunity cost threshold, by health technology category.

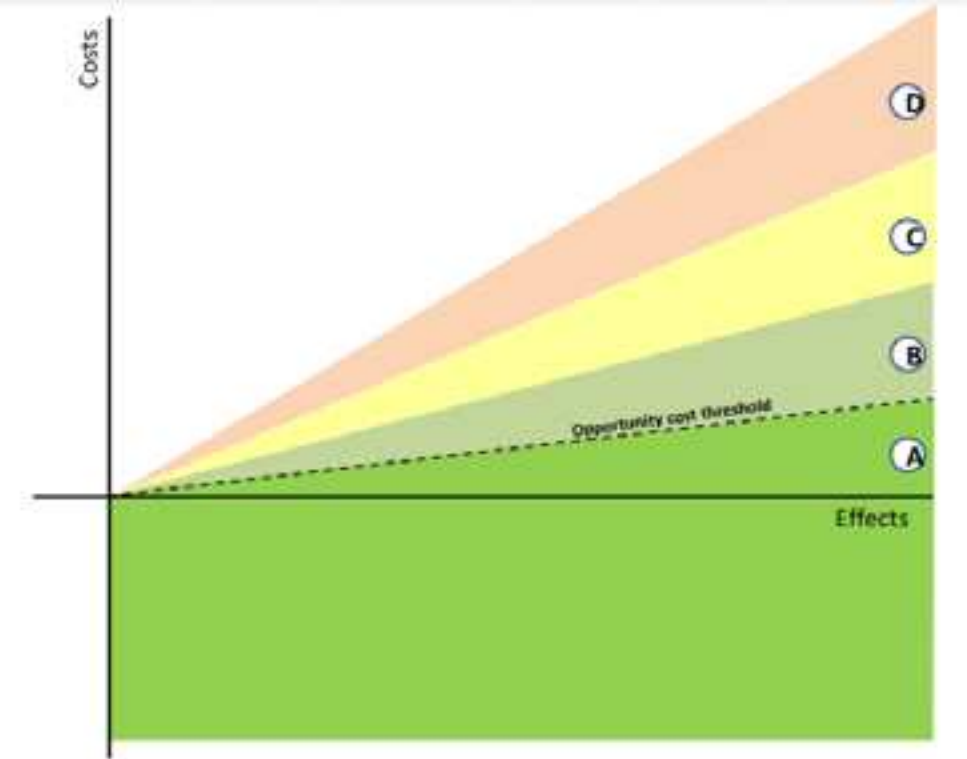


Table 4-1 summarizes the decision rule to determine whether the cost-effectiveness of a health technology can be considered acceptable within each category. The ranges of values are estimated as multiples of the opportunity cost. For example, as seen in the table, according to this decision rule, a technology in category C could be considered cost-effective if its ICER is below 2.5x the opportunity cost.

Table 4-1 Ranges in which the cost-effectiveness of a healthcare technology in each category (expressed as multiples of opportunity cost - OppC) could be considered acceptable

| Category A | Category B | Category C | Category D |
|---|--|--|---|
| From cost saving to a maximum 0.75 OppC | From cost saving to a maximum 1.5 OppC | From cost saving to a maximum 2.5 OppC | From cost saving to a maximum of 5 OppC |
| OppC: opportunity cost | | | |

OppC: opportunity cost

We will now describe the different categories in greater detail and provide examples. For simplicity's sake, we will assume that the country has already determined the criteria or dimensions of value considered relevant based on the health system's objectives and other underlying social values (see Chapter 2). For example, let us assume that a country has defined the following elements as part of its value framework: magnitude and relevance of clinical benefit (effectiveness); quality of the evidence; cost-effectiveness; budgetary impact; impact on equity; impact on public health; severity of the disease; absence of therapeutic alternatives; and costs to patients and their family.

When evaluating the inclusion of a technology, the health system considers all these dimensions. When we say a technology performs well in relevant dimensions according to the local value framework, it means that these dimensions were evaluated and that the technology's performance was considered acceptable.

A - Health technologies or interventions that are cost-saving or are clearly cost-effective according to the local opportunity cost threshold.

As effective and clearly cost-effective technologies, Category A technologies should be included without delay. Their coverage or inclusion in the benefits package will represent a net health gain: from the standpoint of maximizing health benefits, their inclusion is the right decision.

However, health systems may consider other dimensions that could justify not covering a cost-effective health technology or intervention. An extremely negative performance in some dimension, such as an extremely high budgetary impact that threatens sustainability, an increase in inequity, or a technology considered of low social value is reasonable cause for not covering effective and cost-effective technologies.

When released on the market, the HPV vaccine for the prevention of cervical cancer was priced several times higher than it is today. Although it was considered a potentially very effective and cost-effective intervention, many countries refused to cover it because of the enormous budgetary impact it could entail. In some countries, the cost of covering this single vaccine was determined to be almost equivalent to the cost of the entire vaccination program that the countries were offering at the time. Once the price of the vaccine was significantly lower, more countries began to include it in their coverage; nonetheless, it is a good example of the importance of budgetary impact in decision-making. The new hepatitis C drugs also put health systems around the world in a similar situation, in some cases refusing or delaying their coverage due to the high budgetary impact they represented, despite being considered effective and cost-effective.

Another justifiable rationale for non-coverage of technologies in this category is a negative impact on equity. In Thailand, it was determined that the use of dental implants instead of removable dentures could be an effective and cost-effective intervention for improving quality of life. However, a large proportion of the country's population still lacked access to that standard of care. This was especially true in the rural populations with less access to the health system. It was determined that expanding coverage to include dental implants could increase inequality, since it would be mainly the urban population that would end up accessing this service, when large swaths of the population would continue without access to more basic care. It would therefore be inappropriate to include dental implants until broader coverage of more basic interventions for the entire population had been achieved. Expanding the coverage of low- or medium-priority services before there is near-universal

coverage of high-priority services is considered an ethically unacceptable concession that health systems should not make (WHO 2014).

Finally, the coverage of medications for erectile dysfunction (i.e., sildenafil), surgery for tattoo removal, or other cosmetic surgeries are examples of interventions that can be cost-effective but that many health systems around the world decide not to include in their coverage because they consider them to be of low social value.

In summary, category A includes technologies that have proven to be cost-saving or clearly cost-effective according to the local opportunity cost threshold. That is, there is high certainty that their ICER is less than the opportunity cost for that health system (that is why the ICER must be equal to or less than 0.75 of the opportunity cost). With these technologies, the course to follow should be to include them without delay, and the analysis should focus only on ruling out clear reasons why they should not be covered. Simply put, the decision rule would say: it is included in the coverage, unless there are clear reasons to the contrary.

B - Health technologies or interventions that perform well in dimensions considered relevant according to the local value framework and that could be covered despite lack of an optimal cost-effectiveness profile

Category B includes health technologies or interventions that offer significant benefits in clinical outcomes considered relevant, such as improvement in survival or quality of life, and that also perform well in other dimensions of the local value framework. One example could be an effective intervention or technology that is expected to have a positive impact on equity, is aligned with national health priorities, and for which there is little uncertainty when estimating its health benefits and incremental cost-effectiveness ratio. In these cases, coverage within certain limits could be considered, despite the lack of an optimal cost-effectiveness profile.

As discussed above, it is not uncommon for countries to accept a threshold above the opportunity cost, so in this guide we propose as a reasonable limit for this category that the ICER be within a maximum of 1.5x the estimated opportunity cost for that health system.

The technology's performance in the dimensions assessed according to the local value framework will determine the extent to which its coverage can be considered acceptable despite having an ICER that is higher than the opportunity cost of the health system. The better its performance, the greater the likelihood it will be accepted with an ICER at the top end of this category (1.5x the opportunity cost). This means that the fact that a health technology has an incremental cost-effectiveness ratio within the range of this category is a necessary, but not sufficient, condition for it to be considered for coverage.

C - Special cases of effective health technologies or interventions for severe life-threatening diseases that may not be cost-effective according to the local opportunity cost threshold

Category C includes effective health technologies or interventions for serious life--threatening diseases (i.e., with a life expectancy of less than two years). Within certain limits, these technologies could be covered in special cases, despite not being cost-effective according to the local opportunity cost threshold, if the following conditions are met:

- They perform well in dimensions considered important according to the local value framework

- There is reasonable certainty that the new technology can offer a substantial improvement in terms of improved life expectancy (with sufficient quality of life to make this extension desirable) or quality of life. For example, a lower boundary of the confidence interval for estimating improvement in overall survival of at least 0.25 years of life or its equivalent in QALYs; or the intervention is a necessary bridge to another effective treatment.
- It affects a small population and does not represent a high budgetary impact
- There are no other therapeutic alternatives

The degree of clinical benefit and performance of the technology in the dimensions evaluated will determine the extent to which its cost-effectiveness is considered acceptable within the threshold range for this category. Based on the decision rules that other countries apply in these cases, in this guide we propose as a reasonable ceiling for this category that the ICER be a maximum of 2.5x the estimated opportunity cost for that health system. As mentioned earlier, this category includes effective treatments for severe life-threatening diseases but could also include treatments for other illnesses considered a priority by society in each country.

D – Special cases of effective health technologies or interventions for severe ultra-rare, serious life-threatening diseases that may not be cost-effective according to the local opportunity cost threshold

- They perform well in dimensions considered relevant according to the value framework
- There is reasonable certainty that the new technology can offer a substantial benefit in terms of improved life expectancy (with sufficient quality of life to make this extension desirable) or quality of life. For example, a lower boundary of the confidence interval for estimating the improvement in overall survival of at least 0.5 years of life or its equivalent in QALYs.
- It affects a small population and does not represent a high budgetary impact
- There are no other therapeutic alternatives

The degree of clinical benefit and performance of the technology in the dimensions evaluated will determine the extent to which its cost-effectiveness is considered acceptable within the threshold range for this category. According to the decision rules that other countries apply in these cases, in this guide we propose 5x the estimated opportunity cost for the health system as a maximum ceiling for this category. This is a very special category, which can involve very different health conditions and technologies, and therefore, a wide range is being proposed.

However, the upper limit of this range (5x the opportunity cost) would only be acceptable for technologies that offer maximum health benefit to patients (i.e., more than 10 QALYs).

4.5. Application in Latin American countries

Table 4-2 presents the estimate of the threshold or upper limit for considering the cost-effectiveness of a health technology acceptable in each category in several Latin American countries. Values were obtained from each country’s opportunity cost estimates (Chapter 3) and the proposed decision rule for each category as multiples of the opportunity cost (Table 4-1).

Table 4-2 Threshold or upper limit for considering the cost-effectiveness of a health technology acceptable in each category (in US\$ 2016 and as a fraction of GDP)

| Country | Category A | Category B | Category C | Category D |
|-------------|-------------|--------------|--------------|--------------|
| Argentina | 8,397 (0.7) | 16,793 (1.3) | 27,989 (2.2) | 55,978 (4.4) |
| Belize | 2,575 (0.5) | 5,149 (1.1) | 8,582 (1.8) | 17,165 (3.5) |
| Bolivia | 1,704 (0.6) | 3,408 (1.1) | 5,680 (1.8) | 11,360 (3.7) |
| Brazil | 6,451 (0.7) | 12,901 (1.5) | 21,502 (2.5) | 43,005 (4.9) |
| Chile | 8,554 (0.6) | 17,109 (1.2) | 28,515 (2.1) | 57,030 (4.1) |
| Colombia | 2,991 (0.5) | 5,983 (1.0) | 9,972 (1.7) | 19,943 (3.4) |
| Costa Rica | 6,781 (0.6) | 13,562 (1.2) | 22,604 (1.9) | 45,207 (3.9) |
| Cuba | 6,089 (0.8) | 12,178 (1.5) | 20,297 (2.5) | 40,593 (5.0) |
| Ecuador | 3,692 (0.6) | 7,384 (1.2) | 12,307 (2.0) | 24,613 (4.1) |
| El Salvador | 2,226 (0.6) | 4,452 (1.2) | 7,420 (2.0) | 14,839 (3.9) |
| Guatemala | 2,115 (0.5) | 4,230 (1.0) | 7,050 (1.7) | 14,099 (3.4) |
| Honduras | 1,440 (0.6) | 2,880 (1.2) | 4,800 (2.1) | 9,600 (4.1) |
| Mexico | 4,276 (0.5) | 8,552 (1.0) | 14,254 (1.6) | 28,508 (3.3) |
| Nicaragua | 1,334 (0.6) | 2,667 (1.3) | 4,445 (2.1) | 8,891 (4.2) |
| Panama | 8,135 (0.6) | 16,271 (1.1) | 27,118 (1.9) | 54,236 (3.8) |
| Paraguay | 2,785 (0.5) | 5,569 (1.0) | 9,282 (1.7) | 18,564 (3.5) |
| Peru | 2,991 (0.5) | 5,982 (1.0) | 9,971 (1.6) | 19,942 (3.2) |
| Uruguay | 9,758 (0.6) | 19,516 (1.3) | 32,526 (2.1) | 65,052 (4.2) |

Note: Estimates are based on the opportunity cost for each country (central estimate, lower and upper boundary) described in Chapter 3.

4.6. Final remarks

Application of the decision rule presented here requires that health systems have a defined value framework and that technologies be evaluated according to this framework, since decisions are not based solely on their cost-effectiveness. The fact that a healthcare technology presents an incremental cost-effectiveness ratio within the range of a given category does not mean that it must necessarily be included in the benefits package and financed.

For example, a new cancer drug that offers unimportant clinical benefits or for which the cost-effectiveness estimate is uncertain or there are doubts about the quality of the evidence may not be covered despite having an ICER within the established maximum for health technologies for serious life-threatening diseases (Category C). This implies that there will be a ranking in each category, so that not all technologies in a given category can aspire to be covered with an ICER at the upper end of this range. This higher end would be acceptable only for technologies whose performance in other dimensions of the value framework is deemed good enough to justify their inclusion.

Expressing cost-effectiveness ranges as multiples of opportunity cost makes these potentially controversial and costly decisions more explicit in terms of population health and enables the benefits lost to each decision to be quantified (Sculpher 2016). Table 4-3 shows what benefits could be obtained, what benefits would be lost, and the net benefit of covering or including a technology whose ICER is at the upper limit of each category in the benefits package. For example, when deciding to finance a new technology at the upper limit of category C (2.5x the opportunity cost), for each unit of benefit obtained thanks to the new technology, the health system will be losing the possibility of obtaining 2.5 units of profit through other technologies or interventions, for a net loss of 1.5 units.

Table 4-3 Benefits obtained, benefits lost, and net benefits from covering technologies at the upper limit of each category

| | Category A | Category B | Category C | Category D |
|-------------------|-------------|------------|------------|------------|
| Benefits obtained | 1 QALY | 1 QALY | 1 QALY | 1 QALY |
| Benefits lost | 0.75 QALY | 1.5 QALY | 2.5 QALY | 5 QALY |
| Net benefits | + 0.25 QALY | - 0.5 QALY | - 1.5 QALY | - 4 QALY |

Clearly defined decision-making rules and modifiers provide a framework for making these difficult decisions and contribute to health resource allocation that more appropriately reflects a society’s values and priorities.

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5.BUDGETARY IMPACT AND AFFORDABILITY THRESHOLD

As mentioned, clinical benefit and cost-effectiveness are often the most important aspects when conducting health technology assessment, but many agencies also conduct budgetary impact assessment studies, which is one of the dimensions frequently included in value frameworks. (See Chapters 2 and 4). When a group of HTA agencies, health decision-makers, and technology manufacturers from Latin America discussed what the most important dimensions of the value frameworks should be, budgetary impact was considered one of the seven basic elements that should not be omitted. (Pichon-Riviere et al., 2019).

There are two important reasons for this. The first is that it is usually necessary to plan the budget to make room for the additional expense that the new technology will entail and thereby ensure that it is adopted in an orderly manner. The second is that beyond being cost-effective, some technologies can create certain additional affordability issues if they represent a high budgetary impact, especially when the health budget cannot be increased in the short term. In these cases, the opportunity cost produced by the technologies that will be displaced to make way for the new technology could be even higher than usual. This is because including a technology with a high budgetary impact in coverage could affect many services and jeopardize their financing.

This chapter will discuss some of the issues related to budgetary impact assessment and how to deal with affordability aspects in the technology onboarding process. It will also propose a guide for determining the value for considering a technology to have a high budgetary impact on each health system.

5.1. Addressing aspects of affordability

Direct-acting antivirals (DAAs) for the treatment of hepatitis C were recently a challenge for the health technology assessment system in the United Kingdom, as they were in many other countries. NICE approved their use in some subgroups of patients based on their cost-effectiveness, but it created major affordability issues for the health system due to the large population of affected patients. Because of this, the English health system delayed adoption of the new regulations while competitively tendering the purchase of DAAs in an effort to lower their price. Similar situations will certainly arise in the future. For example, the emergence of immunotherapies for cancer is transforming terminal illnesses into chronic illnesses; gene therapies or new CAR-T immunotherapies may involve large short-term budgetary outlays rather than spreading them over the lives of these patients. Another controversial aspect related to the evaluation of technologies such as immunotherapy and gene therapies is that both the cost and long-term benefits are uncertain (Drummond et al., 2019).

In these situations, it may be appropriate to enter into risk-sharing agreements based on clinical benefit (Garrison et al., 2013). The design of such agreements, as, for example, in the reform of the Cancer Drugs Fund in the United Kingdom, can be informed by health technology assessment and may be more necessary when it comes to technologies with a high budgetary impact.

After the experience with antivirals for hepatitis C, the United Kingdom introduced a new standard to deal with technologies that could have a high budgetary impact on the health system. This standard makes it mandatory for conversations to be held between the manufacturer and the health system for technologies whose budgetary impact is expected to exceed £20 million per year in the first three years of their adoption. This conversation addresses issues related to pricing, affordability, and payment mechanisms to determine the best conditions for allowing its adoption. This does not mean that the United Kingdom will not allocate more than £20 million per year for the inclusion of a new technology, but it does mean that additional aspects or special payment mechanisms that allow it should be considered. If no agreement is reached, it may mean that the adoption of the new technology will be delayed beyond the usual time in order to cope with the associated budgetary impact. This evaluation is conducted by NICE on a case-by-case basis, fostering conversation between the various stakeholders. These commercial arrangements must be finalized by the time NICE issues the regulations for the technology in question.

Another type of trade arrangement, which was implemented in other European countries, was to relate the price of the product to the volume of its use. In Germany, social security authorized the use of DAAs for a wider range of patients on the condition that manufacturers lowered their price. France reached a similar agreement, in which a lower price was obtained if a certain number of doses were procured. In Australia, the government set a budget ceiling for DAAs.

In the United States, the Institute for Clinical and Economic Review (ICER) includes budgetary impact among its considerations of the “value of a technology” (ICER, 2019). The Institute’s approach takes it into account that the increase in the annual budget allocated to new technologies is limited because private financiers must adapt their coverage to their available budgets. The ICER therefore argues that these short-term budgetary impact considerations should be borne in mind when assessing long-term cost-effectiveness and may sometimes require price negotiation.

Another approach proposed by Lomas et al. for taking these aspects of affordability into account is to consider a lower (more demanding) cost-effectiveness threshold for technologies with a high budgetary impact (Lomas 2018). This argument is based on the fact that the opportunity cost of these technologies is probably not adequately captured at the “usual” threshold due to the large number of technologies that could be displaced.

The indirect financial impact can also be significant. For example, the budgetary impact of including a new cancer drug is generally limited to the cost of procuring it. If the technology is a device, other costs may be involved, such as training or investment in facilities. This is sometimes known as organizational impact and is an increasingly important branch of health technology assessment. Something similar can happen when integrating new practices into existing programs, such as screening or vaccines. A full health technology assessment should consider these costs, which are sometimes not as clear or easy to anticipate.

5.2. Discussion points for Latin American countries

The following are some of the questions that may arise when determining how to take the evidence on the budgetary impact of interventions into account.

(a) How can the budgetary impact assessment be integrated with the assessment of clinical

benefit and cost-effectiveness as a further component of the HTA process?

(b) When considering the per capita health expenditure of Latin American countries in relation to other countries, could a budgetary impact threshold be used as an additional criterion when deciding on the inclusion of technologies?

(c) Should special regulations or agreements be implemented for technologies with high budgetary impact? These regulations could include: establishing a link between the price paid for the technology and the volume used; establishing special contractual arrangements if there are other products that could be competitive; installment payments over longer periods of time for a given technology; requiring that the technology have a better cost-effectiveness profile than the technologies approved by HTA agency's standard procedures; developing performance-based risk-sharing arrangements when the long-term costs and/or benefits of the technology are uncertain.

5.3. When can we say that a technology has a high budgetary impact? Preliminary proposal for a baseline budgetary impact threshold for countries and health systems that have not made their own estimates

Ideally, to determine whether a technology has a high budgetary impact, we should have an affordability threshold that allows us to establish a rule. However, in the case of budgetary impact, there is no consensus on the theoretical basis for establishing this limit. This has not prevented countries from setting values for considering the budgetary impact to be high, and technologies that exceed this limit are subject to additional regulations or requirements.

To propose a guide for the countries of Latin America, it is worth briefly reviewing some international experiences that can be extrapolated to the reality of the region.

International estimates of what is considered high budgetary impact

In England, NICE assesses the financial impact of the introduction of a technology in the first three years. If it exceeds a threshold of £20 million in any of these three years, the health system considers it to have a high budgetary impact. This may involve taking action to mitigate the impact on the health system (NICE Budgetary impact test). This action can include negotiating with the manufacturer of the technology to improve its accessibility, delaying the introduction of the technology, or gradually introducing the technology in different subgroups of patients or indications.

In France, the health system defines a significant budgetary impact as a value of EUR 20 million or more in the second year of a technology's availability or an equivalent impact in terms of organizational impact. (Antoñanzas et al., 2017)

In Germany, rapid access will be permitted for drugs with an annual budgetary impact of less than €1 million, with the added benefit of not being subject to price controls. If a drug for an orphan disease will have an annual budgetary impact of less than €50 million, it may be included through a more direct process with lower requirements, although it must go through the price negotiation process (Antoñanzas et al., 2017). This policy implies that €50 million per year is considered a significant budgetary impact that requires additional mechanisms before allowing the coverage of a technology.

In Australia, the inclusion of medicines with an annual budgetary impact of more than A\$5 million requires a special authorization procedure involving the Ministry of Economy. When the impact is expected to exceed A\$10 million in any of the first four years of use, authorization from the federal government's entire cabinet is required. Different studies estimated that the probability of a drug being covered and included in the benefits package in Australia could fall by up to half if the budgetary impact is higher than the threshold of A\$10 million (Chim et al., 2010; Harris et al., 2008; Mauskopf et al., 2012).

In the United States, ICER developed a methodology for defining high budgetary impact on medicines. If a single molecule implies an annual expenditure of more than US\$904 million at the national level, it is considered to have a high budgetary impact (ICER, 2019). This value arises from assuming that that health expenditure is expected to increase by a certain value (1%) above expected GDP growth (2.75%) and that 13.3% of total health expenditure corresponds to medicines. From these values, and knowing what the total health expenditure is, the total amount that the budget for new medicines could grow each year is estimated. The average of this increase in expenditure, which could correspond to each new molecule, is estimated from the number of new molecules that become available each year (34 in 2016). Any drug whose budgetary impact involves doubling this average value is considered to have a high budgetary impact.

In 2015, Canada developed a mechanism for prioritizing which technologies should be evaluated by the Canadian Agency for Drugs and Technologies in Health (CADTH). This prioritization considers a series of attributes and dimensions of the candidate technologies, such as potential clinical benefit, potential population impact, and equity aspects. In the economic dimension, a budgetary impact of Can\$50 million (CADTH, 2015) is defined as significant impact.

Preliminary estimate of a budgetary impact threshold for jurisdictions without their own estimates

As has been shown, countries express the threshold for determining high budgetary impact as a net value at the national level. This value cannot be compared or transferred directly to other jurisdictions, as it depends on factors such as population size and health expenditure. Even with the same health system and per capita health expenditure, two countries with different populations may not have the same budgetary impact threshold in net terms. It would be unreasonable to expect two countries with a similar number of inhabitants (e.g., Colombia and England) to have the same budgetary impact threshold if their health expenditure is very different (US\$340 vs US\$4,000). Therefore, in order to obtain comparable values, it is preferable to express the budgetary impact threshold as a fraction of health expenditure, calculated as follows:

$$BI_{Frc} = \frac{BI_{Net}}{Pop_{Loc} \cdot HSp_{Loc}}$$

where BI_{Frc} is the estimate of budgetary impact as a fraction of health expenditure and BI_{Net}, Pop_{Loc}, and HSp_{Loc} are the budgetary impact threshold, total population, and health expenditure per capita.

Table 5-1 presents reference values for high budgetary impact used by the countries described

above. The values are expressed as the net value used by the country at the national level, in local currency and as a fraction of health expenditure. As an example, this table also presents the equivalents of each of these high-budgetary impact thresholds transferred to Argentina. To adapt the definitions of high budgetary impact from one jurisdiction to another, the following equation was used:

$$AT_{Local} = \frac{AT_{Ref}}{Pop_{Ref} \cdot HSpc_{Ref}} * Pop_{Local} * Heps_{Local}$$

where AT_{Local} is the estimate of budgetary impact transferred to the local context in net values; AT_{Ref} , Pop_{Ref} and $HSpc_{Ref}$ are the estimate of budgetary impact, total population, and health expenditure per capita in the reference country; Pop_{Local} and $HSpc_{Local}$ are the population and health expenditure per capita of the country to which the estimate is to be transferred.

Table 5-1 High budgetary impact threshold in selected countries

| Country | High budgetary impact threshold (in local currency) | Local currency | As a fraction of per capita health expenditure | Equivalent for Argentina (in USD.) |
|------------|---|-------------------|--|------------------------------------|
| England | 20,000,000.00 | Pounds | 0.00016 | 8,677,566.04 |
| France | 20,000,000.00 | Euros | 0.00004 | 2,169,391.51 |
| Germany | 50,000,000.00 | Euros | 0.00013 | 7,050,522.41 |
| Australia | 10,000,000.00 | Australian Dollar | 0.00008 | 4,338,783.02 |
| ICER - USA | 904,000,000.00 | US Dollar | 0.00028 | 15,185,740.57 |
| Canada | 50,000,000.00 | Canadian Dollar | 0.00019 | 10,429,766.87 |

England’s high budgetary impact threshold of £20 million is equivalent to 0.00016 of the country’s total health expenditure. If a country like Argentina decided to adopt a similar threshold, obviously it would not be able to directly use the value of £20 million, as its population and health expenditure are different. Translating this value with the methodology explained above, the equivalent threshold for Argentina would be approximately US\$8.7million, a value that represents a fraction of health expenditure similar to that of the country of comparison.

The table shows that countries use different definitions and values and that there is no consensus on the methodology for defining high budgetary impact: what should then be the threshold to define it? Beyond variability, it seems reasonable to assume that it is between 0.00008 and 0.00024 units of health expenditure, with a central estimate of 0.00016 units. Based on this estimate, Table 5-2 presents the high budgetary impact threshold values for the country’s total, and per million inhabitants, for a number of Latin American countries (in 2016 current US\$ dollars).

As a reference, the table also presents what it means in each country to cover or include a technology with a high budgetary impact in the benefits package in terms of additional population that could be covered with those same funds. How to interpret this indicator of equivalence between high budgetary impact and additional inhabitants who could receive coverage? In a population of 1,000,000, covering a new technology with a budgetary impact of 0.00016 units of health expenditure represents a budgetary impact equivalent to 160

health expenditures per capita. That is, with the cost of including the new technology in the benefits package, 160 additional people could be covered for all their health expenses; in other words, to finance this new technology, the health system would need 160 additional people to make the average contribution to the health budget but not have any consumption. In the case of Argentina, with a population of 44 million, this means that with the resources that would need to be allocated to cover a new technology with a high budgetary impact, more than 7,000 additional people could receive health coverage (see Table 5-2- with results for all countries).

Table 5-2 Estimates of the high budgetary impact threshold for different Latin American countries (in constant 2016 US dollars), expressed as total net value at the country level, per million inhabitants and as equivalent in number of additional inhabitants who could receive coverage.

| Country | Population | Net threshold of high budget impact at the national level (range) | High budget impact threshold per million inhabitants (range) | Additional inhabitants that could receive health coverage for each technology with high budget impact (range) |
|-------------|-------------|---|--|---|
| Argentina | 44,494,502 | 8,677,566 (4,338,783 - 13,016,349) | 195,026 (97,513 - 292,538) | 7,119 (3,560 - 10,679) |
| Belize | 383,071 | 18,608 (9,304 - 27,913) | 48,577 (24,288 - 72,865) | 61 (31 - 92) |
| Bolivia | 11,353,142 | 386,947 (193,473 - 580,420) | 34,083 (17,041 - 51,124) | 1,817 (908 - 2,725) |
| Brazil | 209,469,333 | 34,049,138 (17,024,569 - 51,073,707) | 162,550 (81,275 - 243,824) | 33,515 (16,758 - 50,273) |
| Chile | 18,729,160 | 3,567,676 (1,783,838 - 5,351,514) | 190,488 (95,244 - 285,732) | 2,997 (1,498 - 4,495) |
| Colombia | 49,648,685 | 2,703,792 (1,351,896 - 4,055,688) | 54,458 (27,229 - 81,688) | 7,944 (3,972 - 11,916) |
| Costa Rica | 4,999,441 | 711,003 (355,502 - 1,066,505) | 142,217 (71,108 - 213,325) | 800 (400 - 1,200) |
| Cuba | 11,338,138 | 1,760,851 (880,426 - 2,641,277) | 155,303 (77,652 - 232,955) | 1,814 (907 - 2,721) |
| Ecuador | 17,084,357 | 1,379,821 (689,911 - 2,069,732) | 80,765 (40,383 - 121,148) | 2,733 (1,367 - 4,100) |
| El Salvador | 6,420,744 | 301,901 (150,950 - 452,851) | 47,020 (23,510 - 70,529) | 1,027 (514 - 1,541) |
| Guatemala | 17,247,807 | 666,048 (333,024 - 999,071) | 38,616 (19,308 - 57,925) | 2,760 (1,380 - 4,139) |
| Honduras | 9,587,522 | 306,117 (153,059 - 459,176) | 31,929 (15,964 - 47,893) | 1,534 (767 - 2,301) |
| Mexico | 126,190,788 | 9,323,715 (4,661,858 - 13,985,573) | 73,886 (36,943 - 110,829) | 20,191 (10,095 - 30,286) |
| Nicaragua | 6,465,513 | 194,646 (97,323 - 291,970) | 30,105 (15,053 - 45,158) | 1,034 (517 - 1,552) |
| Panama | 4,176,873 | 695,482 (347,741 - 1,043,222) | 166,508 (83,254 - 249,762) | 668 (334 - 1,002) |
| Paraguay | 6,956,071 | 364,203 (182,102 - 546,305) | 52,358 (26,179 - 78,536) | 1,113 (556 - 1,669) |
| Peru | 31,989,256 | 1,619,614 (809,807 - 2,429,421) | 50,630 (25,315 - 75,945) | 5,118 (2,559 - 7,677) |
| Uruguay | 3,449,299 | 761,108 (380,554 - 1,141,662) | 220,656 (110,328 - 330,984) | 552 (276 - 828) |

Note: For estimation of the budgetary impact threshold (AT_{Local}), the values corresponding to population and health expenditure (Pop_{Local} and $HEpc_{Local}$) were obtained from the World Bank (<https://data.worldbank.org>) for the last available year (2016). For Argentina, the values for health expenditure correspond to local estimates made by the Ministry of Finance (*). For all estimates, the values of 0.00016, 0.00008 and 0.00024 units of health expenditure per capita per population covered were used for the central estimates, lower limit

and upper limit, respectively.
(*) Secretariat of Economic Policy, Ministry of Finance, Consolidated Expenditure 2004-2015. Available at: https://www.argentina.gob.ar/sites/default/files/gto_publico_consolidado_2004-2015_corrientes.xlsx
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5.4. Final remarks

There is no consensus on a uniform definition of high budgetary impact or how to estimate it. Different countries adopt different definitions, and the implications of exceeding the budgetary impact threshold are different in different systems.

A high budgetary impact is not necessarily a reason not to include a technology in a benefits package, although it may become a reason to reconsider its inclusion, restrict its use to certain subgroups of patients, delay its inclusion or do so in a staggered manner, seek more demanding pricing agreements, extend payments for longer periods, enter into risk-sharing arrangements, or require higher levels of authorization. A high budgetary impact may require consideration of an even more demanding cost-effectiveness threshold (Lomas et al., 2018; Lomas, 2019). On the other hand, the ethical implications of these decisions continue to be a source of discussion (Rumbold et al., 2019).

In low- and middle-income countries, it may be even more important to identify technologies that could have a high budgetary impact and take appropriate action. Indeed, the implications of covering or including these technologies could be even more negative in terms of opportunity cost than in high-income countries. Low- and middle-income countries tend to have less elasticity in budget management because a large part of their budgets is anchored to the payment of salaries or infrastructure maintenance. In addition, fragmentation of the health system can pose an additional problem, since provinces or small states, or social security institutions with relatively few beneficiaries are exposed to a greater risk from high-cost technologies that can jeopardize their sustainability.

Lastly, the final budgetary impact of all additions made to the coverage or benefits package must also be taken into account. The isolated impact of a single technology may not be so significant, but the sum of all the additions could be. Decisions should consider the limits of what the health system is in a position to handle.

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6.USING ECONOMIC EVIDENCE FROM OTHER JURISDICTIONS

Health technology assessments used to inform resource allocation require key information and data elements, many of which may not be available locally. This chapter discusses the use of HTAs from other jurisdictions to focus on economic evidence.

6.1. Key elements of the data to be used

In an analysis of 27 international methodological guides to economic evaluations, Barbieri et al. (2010) examine the key data needed in HTA and the extent to which the data are transferable between jurisdictions, including with regard to clinical clairvoyance, evidence on the use of health system resources, data on health resources, and health status assessments, preferences, or utilities.

The **clinical evidence** used in HTAs consists of two main components: the relative effect of the treatment/technology compared to a relevant alternative; and baseline risk of the disease. The parameters are generally considered independent of one another. Data on the relative effects of treatment typically come from randomized clinical trials or systematic reviews of clinical trials; in most methodological guidelines, these data were considered transferable between jurisdictions. Although it would be ideal to have clinical efficacy data from the jurisdiction itself, in practical terms it is generally impossible to conduct a clinical trial by jurisdiction. However, some of the existing trials may have recruited patients from the jurisdiction in question, or from one with a similar health care system or level of development, and this information could be considered in the HTA. If the technology in question has been used in the jurisdiction itself, even in a limited fashion, it could be verified whether the clinical outcomes obtained from regular clinical use (real-world evidence) are similar to those of international clinical trials, which are conducted predominantly in high-income countries under more controlled conditions.

Baseline risk (e.g., prevalence or incidence of the health problem or outcome of interest) is more likely to vary from jurisdiction to jurisdiction, so it is generally necessary to collect and include epidemiological data from the jurisdiction itself. In fact, in countries without good epidemiological data, one of the first steps to strengthen HTA is to improve local epidemiological data.

The **use of resources in health care** is driven by clinical practice patterns, which may differ both within and between jurisdictions. In many Latin American countries, they may be different even within the same jurisdiction, given the fragmentation of the health system in the public, social security, and private sectors (see Chapter 7.) When conducting an HTA, it is important to understand the local practice patterns relevant to the assessor; this is usually achieved with the participation of doctors or other professionals from the jurisdiction in the team performing the HTA. Observational studies or local surveys may also be necessary. In a survey of HTA agencies in middle-income countries, the fact that most HTAs are conducted in high-income countries was considered a major barrier to their transferability. One of the main reasons was that local clinical practice patterns differed substantially (Drummond et al., 2015). Transferability is also complicated by comparing the new technology with another technology that is no longer used or unavailable in middle-income countries. Although the

latter fact could also limit the usefulness of clinical evidence, today it is possible to make indirect comparisons using meta-network analysis (Hoaglin et al., 2011).

International methodological guidelines significantly agreed on **costs**: HTAs should use local unit costs for relevant health resources. When establishing an HTA agency or system, another priority is to have reliable health system cost data, which often requires an initial investment.

Health status **assessments, preferences, or utilities** are important if local analyses estimate the incremental cost per year of healthy living (either QALY or DALY). When using DALYs, an established value for disability from 234 different health statuses (disability weights) is available; these are “universal” values that come from an international survey in which high-, middle- and low-income countries participated (Salomon et al., 2012). Thus, estimating the incremental cost of a new technology by DALY is usually possible without having to rely on local values or preferences. If results are reported in QALYs, many low- and middle-income countries have studies assessing local social preferences using a generic instrument such as the EuroQol EQ-5D. If a value set for one’s own jurisdiction is not available, one for a similar neighboring country could be used.

6.2. Interpretation and use of HTAs conducted in other jurisdictions

Although the goal should be to conduct HTAs locally, sometimes it may not be possible. In these suboptimal situations, which are common in many countries, the focus could be on seeing what can be learned from HTAs conducted elsewhere. If the plan is to conduct a local HTA, much can be learned from a review of existing studies from other jurisdictions.

There are several resources to assess the transferability of HTAs (Goeree et al., 2010). One of the most important is the HTA adaptation tool of EUNEHTA, European HTA Network (www.eunetha.eu) or “EUNetHTA HTA Adaptation Toolkit”. Ways to use existing HTA studies (and more specifically, economic evaluation) are also discussed in Drummond et al. (2015). It almost never makes sense to apply the result of an existing study directly in the jurisdiction itself, but it is possible to learn a great deal about the particular problems associated with the adoption of the technology in question and the methodological or practical problems in conducting an economic evaluation. There may also be elements of data from an existing study that could be used in the jurisdiction itself.

A few years ago, the Ministry of Health of Chile adapted economic evidence to the local context. To assess the degree of transferability of a number of studies, it used nine specific transferability criteria (Welte et al., 2004): study perspective, discount rate, approach to medical costs, absolute and relative prices in health care, variability of clinical practice, incidence and prevalence, case mix, life expectancy, and inclusion of productivity costs and lost work time. Each criterion was compared with the reference case for economic evaluations in Chile and, according to the degree of agreement, a score was assigned to each criterion, with a maximum score of 12 points. Studies that obtained a score of 10-12 were considered highly transferable (Ministry of Health of Chile, 2016). Methodologies of this type permit the use of economic evidence data not generated in the jurisdiction itself.

6.3. Abbreviated “rapid screening” process for low- and middle-income countries

Given the wide range of HTAs conducted around the world, it would be useful to develop some “speedy sifting” approaches that can help a Latin American or other middle- or low-income countries identify the existing and available HTA reports that are most relevant, whose results may be more informative. The following quick screening questions may serve as a guide.

- Are the health policy and research questions addressed relevant to the questions in your jurisdiction?
- In what language is the report? Is it feasible to translate it?
- Is there an adequate description of the technology being evaluated?
- Is the scope or focus of the evaluation clearly specified?
- Has the report been subject to an external review?
- Is there a conflict of interest?
- When was the evaluation conducted? Is it already outdated for its purpose in your jurisdiction?
- Have the methods used in the HTA report been adequately described?
- Was the study conducted in a country with a level of wealth or health expenditure (GDP per capita/health expenditure per capita) similar to that of your jurisdiction? If so, can the results and/or recommendations be considered relevant for the jurisdiction, either (i) as presented, or (ii) with a basic cost-pricing adaptation or practice patterns?
- Was the study conducted in a country with a higher level of wealth or health expenditure (GDP per capita/health expenditure per capita) than in your jurisdiction? If so:
 - » for studies with negative results/recommendations, can we automatically assume that they could apply to your jurisdiction? (If the technology was not considered cost-effective in a higher-income country, it would probably not be cost-effective in yours)
 - » for studies with positive results/recommendations, can you also automatically assume a negative result/recommendation for your jurisdiction, unless the estimated ICER is less than, say, 2x the opportunity cost in your healthcare system? For drugs or devices where the ICER is usually very sensitive to the cost of procuring the technology, this criterion would imply that it is not worth conducting a local economic assessment unless the manufacturer of the technology is willing to offer a significant discount (i.e., 50% or more) on the usual price of the technology in the high-income country where the HTA was conducted.

6.4. Discussion points for Latin American countries

Countries considering incorporating economic evidence into their decision-making process should consider the following:

- *Are the epidemiological and cost data needed to conduct local economic assessments available, and if not, should investments be made to ensure their availability?*
- *Are there sufficient human resources with the necessary skills to conduct, adapt, and/or interpret economic assessments, and if not, should these capacities be developed at the local level?*
- *Are there international or regional networks that can be used or created to coordinate and facilitate regional and international collaborative activities in the conduct of economic assessments?*

Ideally, countries should be able to move forward by creating the necessary capacities and conditions to have all the elements required for correct decision-making. However, the reality

is that HTA agencies must often issue recommendations on interventions or technologies for which all the necessary information cannot be obtained. This situation is even more common in low- and middle-income countries that do not have the HTA structures or resources to evaluate all interventions or to evaluate all dimensions considered relevant for decision-making. This is particularly true in the economic dimension since, unlike other aspects such as clinical benefit or quality of evidence, assessment of the economic dimension is more context-specific and usually requires a greater intensity of analysis and local data. Even in countries where the necessary technical resources are available, there may be situations in which decisions must be made on a large number of technologies in a short period of time, limiting the ability to conduct full assessments of the economic dimension of all of them. (Teerawattananon et al., 2017)

Economic evaluations in most Latin American countries are not comprehensively and systematically conducted for all technologies for which a decision with regard to their coverage or inclusion in the benefits package must be made.

This is a major constraint since, as we have seen, evidence of cost-effectiveness is one of the key elements. It is common in Latin America for health systems to make coverage decisions without the ability to evaluate this dimension with a local economic evaluation (Pichon-Riviere et al., 2019). In this scenario, data or studies from other jurisdictions can provide relevant information.

Let’s look at the following example of a middle-income country with a GDP per capita of US\$8,000 and per capita health expenditure of US\$600. This country must decide whether to include a new treatment, whose cost per patient is US\$20,000, in its benefits package. There is no information on its cost-effectiveness at the local level, but cost-effectiveness is considered an important dimension that we would like to take into account. Suppose that this treatment has already been evaluated in a high-income country with a GDP and health expenditure per capita of US\$40,000 and US\$3,500, respectively, and the decision was made not to include it in the coverage package because it was not considered cost-effective. The cost of the new treatment is similar in both countries. Unless there are more particular epidemiological or health system situations, at the same price it is highly unlikely that a technology that is not cost-effective in a high-income country will be cost-effective in a lower-income country. If it is important for your country to take the economic evidence into account, given the strong indications about the low probability that it will be cost-effective in your country, it would be reasonable to take this information into account. In the next section we discuss how this type of information could be systematized for use when it is neither possible nor feasible to conduct a local economic assessment.

6.5. Preliminary proposal for a provisional or temporary approach to estimate the likelihood that a technology will be cost-effective in the absence of local economic assessments.

The following approach is based on the methodology developed by the Institute of Clinical and Sanitary Effectiveness of Argentina (IECS; Alcaraz et al., 2017), which is still in the pilot stage and validation process. This methodology evaluates three dimensions, and based on the results of each, assigns a probability that the technology will be cost-effective at the local level through a deliberative process. Some of the dimensions are looked at more objectively, and others require a more evaluative component. The three dimensions evaluated are:

- 1. Analysis of the technology’s coverage or inclusion in benefits packages of other countries
- 2. Crude extrapolation of cost-effectiveness obtained in economic assessments of other jurisdictions
- 3. Estimation of a “restricted cost-effect ratio” based on the clinical benefit and cost of the technology

These three dimensions cannot necessarily be evaluated for all technologies. This will depend, above all, on the information available and accessible. The result of each dimension evaluated will indicate whether evidence from other jurisdictions indicates that the probability that the technology can be considered cost-effective in your environment is very low, low, moderate, or high (see Table 6-1).

Table 6-1 Probability that the technology is cost-effective in the local context (for this particular indication in this group of patients). Example of a hypothetical case.

The sections below describe how to evaluate each of these dimensions and suggest how to integrate each of them into a summary judgment.

| Information on: | Probability that it will be cost-effective | | | | |
|--|--|--------|-----------------------------|-------------|---------|
| | A. Very Low | B. Low | C. Uncertain/no information | D. Moderate | E. High |
| 1 Coverage or inclusion of the technology in other countries | X | | | | |
| 2 Crude extrapolation of cost-effectiveness in other jurisdictions | | X | | | |
| 3 Estimation of "cost-effect" based on clinical benefit and cost of technology | | | | X | |
| Summary judgment: Low probability of being cost-effective | | | | | |

Analysis of coverage or inclusion of technology in the benefits packages of other countries

The probability that the technology or intervention will be considered cost-effective in your environment based on analysis of the coverage of other countries will be categorized as very low, low, moderate, or high (or will be considered uncertain) according to the following parameters:

- a. **Very low:** It is not explicitly covered for the indications evaluated (or was not considered cost-effective*) in three or more countries with higher GDP, and there is no indication that the price of the technology, adjusted for health expenditure per capita, is locally

at least 20% lower than in the reference country or countries.

- b. Low:** It is not explicitly covered for the indications evaluated (or was not considered cost-effective²) in one or two countries with a higher GDP, and there is no indication that the price of the technology, adjusted for health expenditure per capita, is locally at least 20% lower than in the reference country or countries.
- c. Moderate:** It is explicitly covered (or was considered cost-effective) for the indications evaluated in one or two countries with similar or lower GDP within a basket of selected countries (for example, for Argentina the basket of countries to be evaluated could consist of Brazil, Chile, Colombia, Costa Rica, Mexico, and Uruguay), and there is no indication that the price, adjusted for health expenditure per capita, is locally 20% higher or higher than in the reference country or countries.
- d. High:** It is explicitly covered (or was considered cost-effective) for the indications evaluated in three or more countries with similar or lower GDP in a basket of selected countries, and there is no indication that the price, adjusted for health expenditure per capita, is locally higher by 20% or more than in the reference country or countries. In all the examples below, price adjustments based on per capita health expenditure should be made as follows:

where P_A is the adjusted price (equivalent) to the country in question, P_O and Gpc_O are the price and health expenditure per capita in the reference country of origin; and

EQUATION 1

$$P_A = P_O * \frac{Gpc_A}{Gpc_O}$$

Gpc_A is health expenditure per capita in the country to which we are transferring the price. See examples below.

Examples from Costa Rica (GDP per capita US\$11,700 and health expenditure per capita US\$889) provide an illustration. Technology 1 was evaluated by the Technology Incorporation Commission (CONITEC) in Brazil (GDP per capita US\$9,900 and health expenditure per capita US\$1,015), and the decision was made to incorporate it into the coverage of the Unified Health System (known by the Portuguese acronym SUS). The negotiated price of the technology for the SUS in Brazil was US\$1,300, which would yield an equivalent price for Costa Rica, adjusted for health expenditure, of US\$1.139 (Equation 1). If the price of technology in Costa Rica does not substantially exceed this reference price (for example, by 20% or more), this would be an indication that it could be considered cost-effective.

Technology Example 2: A technology priced at US\$2,500 was excluded from coverage by Australia's Pharmaceutical Benefits Advisory Committee (PBAC) (GDP per capita US\$50,000 and health expenditure per capita US\$5,000). The equivalent price for Costa Rica, adjusted for health expenditure (Equation 1), would be US\$445. If the price of the technology in Costa Rica is not substantially lower than this reference price, this could be considered an

² If when deciding whether to include the technology the country deemed that it was not cost-effective, this is the data that must be considered when evaluating this dimension, even if the technology has later been covered or included in the benefits package of the country in question. This is something that happens in some jurisdictions (such as the United Kingdom, Canada, and Australia), where often, the cost-effectiveness result is adverse, but after negotiations (which are usually confidential), the country or province decides to include the technology. The reverse is also true: If the technology was considered cost-effective in a country, this is the data that must be considered, even if it was subsequently not covered due to other considerations. See examples in the text.

indication that it would not be cost-effective.

Technology Example 3: Priced at \$4,500, it was assessed by NICE in England (GDP per capita US\$40,500 and health expenditure per capita US\$3,960) and rejected as not cost-effective. After a series of negotiations with the manufacturer, discounts and special access agreements were reached and the technology was included, but the current price for the English health system is unknown. The equivalent price for Costa Rica, adjusted for health expenditure, based on the public price in England (US\$4,500), would be US\$1,010 (Equation 1). If the price of the technology in Costa Rica is not substantially lower than this reference price, this would be an indication that it would not be cost-effective.

Crude extrapolation of the cost-effectiveness of economic evaluations (EE) conducted in other jurisdictions

Economic evaluations from other jurisdictions should be prioritized as follows: good quality evaluations by other countries in the same region and with a similar GDP, prioritizing evaluations conducted by or presented to public HTA agencies; good quality evaluations conducted in another region in countries with a similar GDP, prioritizing evaluations conducted by or presented to public HTA agencies; and good quality evaluations from other countries, prioritizing evaluations conducted by or presented to public HTA agencies.

The results of the ICER are adjusted to the local context through the price of the technology:

where $ICER_A$ is the ICER adjusted to the country in question, $ICER_O$ and P_O are the ICER and price of the technology in the EE's country of origin; and P_A is the price in the country to

EQUATION 2

$$ICER_A = ICER_O * \frac{P_A}{P_O}$$

which we are moving the ICER.

This very simplified approach is most useful in the case of high-cost technologies (such as cancer drugs) in which the price of the new technology is more likely to represent the largest proportion of the cost differential between the intervention and its comparator. While it has many limitations and involves a very imprecise measurement of what the true ICER might be, it can provide rough information about the likelihood of a technology being cost-effective. Because the decision rules for determining cost-effectiveness are directly related to health expenditure per capita, since a country with higher health expenditure may have a higher cost-effectiveness threshold (see Chapters 3 and 4), if a technology was cost-effective in a country with a health expenditure four times higher, it is likely that it will also be cost-effective in your country if its price is four times lower. This is what this approach is trying to capture, in a very general way.

The probability that the technology or intervention will be considered cost-effective in your environment by extrapolating the cost-effectiveness of evaluations conducted in other jurisdictions will be categorized as very low, low, moderate, or high (or will be considered uncertain) according to the following parameters:

- a. Very low probability:** The adjusted ICER is greater than 2x the cost-effectiveness

threshold defined for that technology and indication in your jurisdiction.

- b. Low probability:** The adjusted ICER is greater than the cost-effectiveness threshold defined for that technology and indication (and less than 2x the threshold) in your jurisdiction.
- c. Moderate Probability:** The adjusted ICER is less than the cost-effectiveness threshold defined for that technology and indication in your jurisdiction.
- d. High Probability:** The adjusted ICER is less than 1/2 the cost-effectiveness threshold defined for that technology and indication in your jurisdiction

Let's look at an example from the perspective of Costa Rica (GDP per capita US\$11,700 and health expenditure per capita US\$889). An economic evaluation in Spain (GDP per capita US\$26,600 and health expenditure per capita US\$2,400) found an ICER of US\$38,000 per QALY for a technology whose price is US\$1,300. In Costa Rica the price of this technology is US\$650, resulting in an adjusted ICER of US\$19,000 (Equation 2). According to Costa Rica's opportunity cost threshold (US\$9,041 – see Chapter 3), this intervention would not be cost-effective. However, we believe that this is a very effective cancer drug to improve the overall survival of patients, so Costa Rica could eventually consider its coverage up to a threshold of US\$22,604 (based on the decision modifiers, it is a category C technology, so in our example, society could agree to pay up to 2.5 times the opportunity cost threshold. See Chapter 4). In this case, this would be an indication that there is a moderate probability that it will be cost-effective in Costa Rica, since the adjusted ICER is within the threshold range considered acceptable for this category. If the price in Costa Rica were at an even lower value – for example, less than US\$400, this could be considered an indication of a high probability that it will be cost-effective, as the adjusted ICER would fall to less than half of this category C threshold.

Estimation of a “cost-effect ratio” based on the results of clinical studies.

This approach could be considered in the case of technologies targeting serious illnesses with reduced life expectancy, in which the technology would be expected to produce a benefit considered relevant in terms of increasing overall survival and/or adjusted for quality of life, and when, given the high price of the technology in relation to the cost of managing the illness, the incremental cost of the new technology is considered to represent the largest proportion of the cost differential between the new intervention, which includes the technology in question, and the relevant comparator(s) in your jurisdiction.

Estimation of the “cost-effect ratio” is based on the difference between the local cost of treatment with the new technology and its comparator, and the effect observed in clinical trials when information is available on the impact of the technology in terms of overall survival and/or survival adjusted for quality of life. This approach could be applied in the case of technologies whose observed benefit in randomized controlled trials is greater than 3 months of overall survival (or its equivalent in terms of survival adjusted for quality of life). In such cases, where there were no global survival data and/or QALYs, and if considered appropriate, the estimate of overall survival could be based on the available progression-free survival data (e.g., difference in overall survival equivalent to one-third of the difference in progression-free survival), although this point is more controversial.

An example, again from the perspective of Costa Rica (GDP per capita US\$11,700 and health expenditure per capita of US\$889): a study considered to be of very good quality that compared the new treatment with the customary treatment, found a significant improvement in survival (1.2 additional years of life), with a degree of uncertainty considered reasonable

(CI95%, 0.8 to 1.4 years). The cost per patient of this new treatment, which is combined with the current treatment, is US\$14,000; therefore, it does not significantly replace expenses for other treatments. The “cost-effect” ratio will be US\$-11,700 (14,000/1.2) per year of life, which would not be cost-effective according to the opportunity cost in Costa Rica. If classified in category B as presented in Chapter 4, it could then be considered that there is a moderate probability that it will be cost-effective, since it is within the limits of the threshold defined for this category in Costa Rica (US\$13,500, or up to 1.5 GDP per capita per QALY).

At the other extreme, a drug that offers only a modest improvement in survival (0.3 QALYs) at a cost of US\$20,000 would be indicative of a very low probability of being cost-effective in Costa Rica, since its cost-effectiveness ratio more than doubles the threshold, even in category C.

How to consolidate the information surveyed?

Table 6-1 presented an example of what the results of the information survey for a hypothetical technology could be. As we can see, it may be the case to find discordant information, in some cases indicating a greater or lesser probability of cost-effectiveness at the local level. This is to be expected, because these are very approximate measures. The information should be integrated into a summary conclusion through a deliberative process that can take other characteristics of the information gathered into account (such as the degree of confidence in the results, similarity to the countries from which the information was obtained, etc.).

It is important to point out again that this guidance is indicative and should be tailored to the local decision-making context. For example, the more “unique” the health technology status for the particular indication(s) for your jurisdiction, the less that information from other jurisdictions may be extrapolated. In this vein, the approach described could not be applied or would have even more limitations in case of technologies related to local or endemic health problems (e.g., Chagas disease in some LAC countries), since this limits the ability to extrapolate information from other contexts.

So far, we have discussed how to evaluate the probability that a technology will be cost-effective in your jurisdiction in the absence of local studies. Next, we will propose an approach to integrate this piece of information with other domains such as the quality of evidence, magnitude of benefit, budgetary impact, and other local contextual factors. The objective is to establish whether the information we have is favorable, unfavorable, or uncertain regarding the decision on coverage or inclusion of the technology in the benefits package.

Economic evidence could be considered favorable to the inclusion of technology under the following conditions:

- 1. A good quality economic evaluation performed locally shows that the technology is cost-saving; or
- 2. A good quality economic evaluation performed locally shows that the technology is cost-effective according to the decision rule for its category and does not represent a high budgetary impact; or
- 3. There is no good quality economic evaluation performed locally, but **all** of the following conditions are met:
 - a. The magnitude of the benefit is considered relevant and the quality of evidence is considered appropriate;

- b. It does not represent a high budgetary impact;
 - c. The evaluation of the probability that it is cost-effective is considered high according to indirect estimates;
- Or **all** the following conditions:
- d. The incremental cost that the technology represents with respect to its comparator is not high;
 - e. The affected population is small;
 - f. The magnitude of the benefit is considered relevant and the quality of evidence is considered appropriate;
 - g. It does not represent a high budgetary impact; and,
 - h. The evaluation of the probability that it is cost-effective is not considered low or very low according to indirect estimates.

Economic evidence could be considered unfavorable to the inclusion of technology under the following conditions:

- a. A good quality economic evaluation performed locally shows that the technology is not cost-effective; or
- b. The assessment of the probability of its being cost-effective is considered very low according to indirect estimates; or
- c. The assessment of the probability that it will be cost-effective is considered low according to indirect estimates, and the incremental cost that the technology represents with respect to its comparator is high or represents a high budgetary impact.

Finally, the economic evidence regarding the inclusion of the technology could be considered uncertain when none of the conditions described in the previous categories are met.

6.6. Final remarks

In this chapter we try to outline a possible proposal for integrating economic evidence - almost always from other jurisdictions - into decision-making in your jurisdiction. It is not intended to be used routinely in all decisions to cover or include technologies in the benefits package, since it is not advisable to introduce technologies or interventions without knowing with certainty their cost-effectiveness at the local level. However, this information could be useful in many circumstances where requiring or conducting comprehensive economic evaluations is not possible. It can also serve as a guide for the final decision to incorporate or reject a technology under conditions where preliminary decisions must be made before a proper assessment of local cost-effectiveness is available.

If such a process is used to temporarily decide whether to reject or include a local technology on the basis of “indirect” economic evidence, it is suggested that the follow-up of these decisions be in some way different from decisions made with local economic evidence. When deciding to include a technology without direct economic evidence, it could be done within a supervised framework in which its performance in the jurisdiction in question and its cost-effectiveness at the local level can be monitored. This process can also aid in the development of special contracting and purchasing models for cases in which a preliminary decision or one with a high degree of uncertainty is made that exceeds what is discussed in this document but may include mandatory records to monitor performance, risk-sharing agreements, and greater restrictions on its indication (for example, limiting its indication to certain services or hospitals).

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7.IMPLEMENTATION OF HTAs IN FRAGMENTED HEALTH SYSTEMS

Most Latin American countries have fragmented health systems, where public, social security, and private subsystems, or state or provincial health systems, coexist with significant autonomy. This contrasts with countries where HTA is more established, as is the case in Europe, Canada, and Australia. Many of these countries have a “single payer,” the national health system. Others have a national insurance system or an integrated social security sector with multiple payers acting in a coordinated manner (for example, they may have a national list of covered drugs). In these countries, the role of HTA is clearer, in the sense that a single technology assessment can inform and affect a wide range of policymakers across the entire health system at the national level. In a fragmented system, in contrast, conducting and using health technology assessment involves some challenges. This chapter identifies and discusses some aspects of the use of HTA in fragmented health systems and proposes a number of practical elements to bear in mind when conducting HTAs in these contexts.

7.1. Challenges in fragmented health systems

The most obvious difference between decision-makers in different fields is that they may have different information or data needs for HTA and/or the decision-making process. The cost structure may be different in the various subsectors or regions, which implies that the HTA should, for example, include an interactive model that allows decision-makers to use their own cost data. The same may hold true for other parameters. On the other hand, if therapeutic alternatives for the technology in question vary from sector to sector, it may be more difficult for an assessment to provide the necessary information for everyone. For example, it may be that treatments are being used in the private sector that are not yet used in the public sector. In that case, the incremental cost-effectiveness ratio is going to be different in those subsectors because it will refer to different comparators.

Since each sector is independent, different decision rules are likely to apply when including new technologies. This may affect the use or relevance of the health technology assessment. A critical point is the use of a cost-effectiveness threshold. If the cost-effectiveness threshold is related to the opportunity cost, the threshold may differ from subsector to subsector.

The potential impact of these different thresholds by subsector or region has already been discussed in Latin America (Lamfre et al., 2018). A study by RedArEts (Network of non-profit public institutions dedicated to the evaluation of health technologies in Argentina) found that the incremental cost-effectiveness ratio of colon cancer screening in patients aged 50-75 could vary from 0.15 to 0.42 GDP per capita per QALY depending on the province analyzed (Hasdeu et al., 2017).

The existence of different thresholds within a country or region is not an unsolvable problem. A single assessment can be conducted and subsequently tailored to the various subsectors (i.e., using a model that allows decision-makers to use different parameters for each sector); different decisions can then be made on whether to include the technology in each sector. This usually occurs in fragmented or heterogeneous health systems, either with or without

HTAs. Typically, newer treatments are more likely to be available in the private sector rather than the public sector, or in large urban centers rather than rural areas. If per capita health expenditure is higher in the private sector than the public sector, it is possible that using the same evaluation, a technology is cost-effective in the private sector and therefore included but not so in the public sector, or included in both sectors but with different prices. In other cases, it is more complicated for a single assessment to be relevant to all policymakers; for example, when the customary care (therapeutic alternatives or comparators for the pathology in question) is different in different subsectors.

In addition to the technical difficulties, there are the political ones. Currently, different subsectors make different decisions about the inclusion of technologies. However, if a more explicit decision-making process begins to be implemented using HTA, and the heterogeneity among sectors is explicitly taken into account – for example, using different thresholds – these differences will become more visible, which can be politically sensitive. A potential advantage is that having different thresholds does not necessarily imply differences in access: they can be used to achieve lower prices in sectors or regions with lower health budgets (and therefore lower thresholds). Another positive aspect is that the introduction of HTAs can be used to achieve greater convergence toward a more unified and transparent decision-making process among the different subsectors, if this is a political goal – for example, in countries moving toward universal health coverage. In the medium and long term, this will probably end up promoting greater convergence of the thresholds used by the different subsectors in the decision-making process, and consequently, greater convergence in access and budgets as well. The use of HTAs will make these differences among subsectors more visible and quantifiable and will be able to inform regulatory decisions and policies to achieve greater equity.

Finally, implementation of HTAs in any jurisdiction will lead to greater transparency in the decision-making process. Studies in different countries show that this level of transparency in decision-making processes varies widely (Drummond et al., 2008). There is no “adequate” level of transparency, but it should be borne in mind that this level may differ among sectors in the same jurisdiction (i.e., the private sector may limit transparency due to business confidentiality).

7.2. Discussion points for Latin American countries and preliminary proposal of a methodology for estimating the opportunity cost in different health subsectors

The following are some of the questions that may arise when countries with fragmented health systems seek to include HTAs in their decision-making processes.

- a. *How can HTA documents, including the economic assessment component, be made in the most adaptable/transferable way possible so that they can be relevant to different sectors in fragmented health systems?*
- b. *How are decision-makers in different health sectors currently making decisions on the introduction or rejection of new technologies, and how are HTAs expected to be useful in informing this decision-making?*
- c. *Should discussions be opened on the use of cost-effectiveness thresholds, especially on whether it is necessary to set different values for each sector? If so, should these thresholds remain different over time, or would they be expected to converge in the*

- long run?*
- d. *How politically feasible is the explicit use of different cost-effectiveness thresholds by subsector?*

Tailoring thresholds to different subsectors within the same country

The previous chapters proposed preliminary estimates of opportunity cost thresholds, budgetary impact, and decision-making modifiers or rules for the countries of the region. This section will issue a preliminary proposal to tailor these thresholds to different contexts within a country, whether different health subsectors, geographical areas, or something else, based on per capita health expenditure.

In order to apply this approach, it is necessary to know the per capita health expenditure for each subsector or region – information that is not always readily available. Its estimation involves a number of complexities, since the per capita health expenditure of a given subsector is made up of a series of components, all of which must be considered. For example, per capita health expenditure on social security in a given country consists of:

- The contributions and deductions made by employees and employers, in addition to other contributions or subsidies that may eventually be received (from the state, for example) and are intended for health (excluding, for example, benefits such as pensions or vacation pay)
- The out-of-pocket expenditure of beneficiaries, which in some countries in the region may account for a very high proportion of total health expenditure
- The proportion of public expenditure on health that (directly or indirectly) targets the population covered by social security: e.g., expenditure such as health promotion campaigns or certain vaccines; or expenses for institutions such as the medicines regulatory agency or national institutes; or public sector direct health care expenditures used by social security beneficiaries (e.g., in rural areas where the only health effectors are in the public sector)

In order to estimate the thresholds by subsector, it is necessary to begin by obtaining estimates of how much the health expenditure per capita represents in each subsector. In some cases, health expenditure by region, state, or province could be approximated based on GDP per capita. Based on the data on health expenditure per capita for the subsector or region, the different thresholds may be derived using the following approximation:

$$S_{est} = \frac{C_{est} \cdot S_{HEpc}}{C_{HEpc}}$$

where S_{est} is the parameter estimate for a specific sector; C_{est} is the estimation of the parameter at the country level; S_{HEpc} is the health expenditure per capita in the sector in which the estimate is to be made; and C_{HEpc} is the per capita health expenditure at the country level. Table 7-1 shows, by way of example, the extrapolation of opportunity cost and high budgetary impact thresholds to different subsectors of Argentina.

Table 7-1 Estimate of opportunity cost threshold and budgetary impact by subsector in Argentina (US\$ 2016)

| | Population | Per Capita Health Expenditure (US\$) | Estimated opportunity cost (US\$) | Budgetary impact threshold (US\$) | | |
|-----------------|------------|--------------------------------------|-----------------------------------|-----------------------------------|-----------------|-------------------|
| | | | | Total | Person per year | c/100,000 covered |
| Argentina | 43,417,765 | 1,218.91 | 11,195.62 | 6,830,604.81 | 0.16 | 15,732.28 |
| Public Sector | 11,501,366 | 881.71 | 8,098.48 | 1,308,870.73 | 0.11 | 11,380.13 |
| Social Security | 25,778,456 | 1,163.11 | 10,683.14 | 3,869,898.27 | 0.15 | 15,012.14 |

Note: Per capita health expenditure values by subsector are preliminary estimates currently under development

Table 7-2 shows the potential impact on cost-effectiveness thresholds of applying different opportunity costs per sector in Argentina for the categories and decision rules described in Chapter 4,.

Table 7-2 Threshold or upper limit to consider the cost-effectiveness of a health technology acceptable in each category in the different health subsectors in Argentina: central estimate and lower and upper limit (US\$ 2016 and as a fraction of GDP)

| Sector | Category A | Category B | Category C | Category D |
|-----------------|----------------------------|-----------------------------|-----------------------------|-------------------------------|
| Public Sector | 6,074 (0.5) | 12,148 (0.9) | 20,246 (1.6) | 40,492 (3.2) |
| | [4,049 (0.3)-5,399 (0.6)] | [8,098 (0.6)-16,197 (1.3)] | [13,497 (1.1)-26,995 (2.1)] | [26,995 (2.1)-53,990 (4.2)] |
| Social Security | 8,017 (0.6) | 16,025 (1.3) | 26,708 (2.1) | 53,416 (4.2) |
| | [5,342 (0.4)-7,122 (0.8)] | [10,683 (0.8)-21,366 (1.7)] | [17,805 (1.4)-33,610 (2.8)] | [33,610 (2.8)-71,221 (5.6)] |
| Private Sector | 14,362 (1.1) | 28,724 (2.2) | 47,873 (3.7) | 95,746 (7.5) |
| | [9,575 (0.7)-12,766 (1.5)] | [19,149 (1.5)-38,299 (3.0)] | [31,915 (2.5)-63,831 (5.0)] | [63,831 (5.0)-127,662 (10.0)] |
| Total Argentina | 8,397 (0.7) | 16,793 (1.3) | 27,989 (2.2) | 55,978 (4.4) |
| | [5,598 (0.4)-7,464 (0.9)] | [11,196 (0.9)-22,391 (1.8)] | [18,659 (1.5)-37,319 (2.9)] | [37,319 (2.9)-74,637 (5.8)] |

As can be seen, the implications for decision-making can be very substantial. For example, a cancer drug that offers a significant improvement in overall survival (category C) could be considered cost-effective up to a maximum of US\$20,246 per QALY in the public sector, but this limit could reach up to US\$47,873 in the private sector.

7.3. Final remarks

Using different thresholds for different sectors has technical, political and ethical implications. Not all jurisdictions will necessarily want to move in this direction, nor can it be recommended as the way forward for all countries with fragmented systems. However, it is likely that different decisions are now being made by sector in all countries with fragmented systems. These decisions may be more or less explicit, but they are surely being reflected in different levels of access to health services by the beneficiary populations of the different subsectors or regions.

Therefore, regardless of whether the decision to use different thresholds is made, estimating the opportunity cost in each subsector or region, these thresholds are necessary to help decision-makers appreciate the implications of health decisions – above all, in terms of how much benefit the system as a whole will gain or lose by including a certain technology or

intervention in the coverage plan (Sculpher et al., 2017). In the example of the cancer drug mentioned above, knowing the value at which it can be cost-effective in each subsector can lead to more efficient price negotiations. Making decisions without knowing the opportunity cost for each subsector or region implies ignoring not only the health impact of the decisions but the degree of equity or inequality that they imply.

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APPENDIX I - Preparation of the preliminary report for Argentina

In 2019, Argentina was discussing the potential creation of a Health Technology Assessment Agency. In this context, the IDB asked the authors of this document for a report focusing on some of the key technical aspects that an HTA agency might have to address in its first two years of existence, especially in terms of the use of economic evidence for decision-making on the allocation of health resources.

For the preparation of this report for Argentina, a series of key actors were identified, and meetings were held with the aim of achieving a document that took different perspectives and the country and regional context into account. These actors included patient and user representatives, health funders, national and/or regional government policymakers and regulators, industry, academia, and HTA units or agencies. They were brought together to hear their opinions, bring new perspectives, and enrich the discussions. This interaction included invitations to submit relevant material, two in-person discussion and work meetings on the drafts of the document, and a public event to present the preliminary findings to a wider audience, as detailed in the activities schedule below:

| Date | Activity |
|-----------------------|---|
| 2 August 2019 | Briefing on the objectives, methods, and schedule for the preparation of the document, with the different actors invited to provide documents and information they considered relevant. |
| 2-20 August 2019 | Receipt of material |
| 13 August 2019 | Distribution of the first draft of the document for comments. |
| 16 August 2019 | Webinar to address questions and receive comments on the document. |
| 20 August 2019 | In-person presentation of the preliminary document with Prof. Michael Drummond and the group of institutions and experts for discussion and comments. |
| 22 August 2019 | Public event to present and discuss topics related to the preparation of the document: "International Seminar II - Towards the creation of a National Agency for the Evaluation of Health Technologies in Argentina. How to make decisions about coverage and allocation of health resources. The role of economic evidence: international panorama and situation in Argentina". National Academy of Medicine |
| 10 October 2019 | Distribution of a new version of the document for comments |
| 16 October 2019 | In-person meeting with the group of institutions and experts to present the new version of the document for discussion and comments. |
| October-November 2019 | Receipt of feedback on the latest version of the document |
| February-April 2020 | Preparation of the outcome document |

Note: All actors did not necessarily participate in all stages

Note: All actors did not necessarily participate in all stages

It is important to note that, although the perspectives and contributions of all participants were considered in the preparation of this document, its content is ultimately the authors' responsibility and does not necessarily reflect the opinion or position of the organizations, institutions, experts and/or referents consulted.

Institutions and organizations invited to participate:

Ministry of Health, Ministry of Health and Social Action, Argentina: National Commission for the Evaluation of Health Technologies, Directorate of Health Economics (CONETEC), Directorate of Quality, Patient Representatives at CONETEC; Inter-American Development Bank (IDB); National Administration of Drugs, Food, and Medical Technology of Argentina (ANMAT); Superintendency of Health Services (SSS); National Institute of Social Services for Retirees and Pensioners (INSSJP-PAMI); Federal Health Council (COFESA); Council of Provincial Works and Social Services of the Argentine Republic (COSSPRA); Argentine Network for Health Technology Assessment (RedArETS); Obra Social para el Personal de Obras y Servicios Sanitarios (OSOSS); Federación Argentina de Mutuales de Salud (FAMSA); ISALUD University; Institute of Clinical and Health Effectiveness (IECS); Association of Private Medicine Entities (ADEMP); Asociación Civil de Actividades Médicas (ACAMI); Business Chamber of Pharmaceutical Laboratories (COOPERALA); Argentine Chamber of Medicinal Specialties (CAEMe); Chamber of Medical Diagnostic Institutions (CADIME); Industrial Chamber of Argentine Pharmaceutical Laboratories (CILFA), Argentine Chamber of Supplies, Implantables, and Medical Equipment (CADIEM).

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